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FRACTURES OF THE SPINE.[1]

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THE subject of fractures of the spine has attracted much attention in recent years. The Great War was responsible for innumerable opportunities for the study of these injuries, and especially of the results of neural damage. The enormous advances in motor transport and the mechanization of industry have added vastly to the annual list of injuries of all kinds, including those of the spine. In countries such as ours, where surfing and swimming are becoming more and more popular, an increasing number of accidents are recorded each summer, many of which are fatal, as the result of diving into shallow water.

[1] Read at a meeting of the New South Wales Branch of the British Medical Association on May 27, 1937.

When injuries of the spine are being considered, attention is usually confined to the movable vertebræ, that is, to the cervical, thoracic and lumbar vertebræ. The fixed vertebræ, which in the adult unite to form the sacrum and the coccyx, are regarded as components of the pelvic girdle, and fractures of these are usually classed with fractures of the pelvis. However, the figures from the Royal Prince Alfred Hospital, which I shall put before you later, will include fractures of the sacrum and coccyx.

The movable vertebræ, with the exception of the first (atlas) and second (axis), have certain common characteristics. Each consists of an anterior part (the body) and a posterior part (the vertebral arch), which together enclose the vertebral foramen. The atlas differs in having no body, while the axis, though possessed of a body, has projecting from its upper aspect the odontoid process, which represents the body of the atlas.

In the articulated vertebral column the bodies form a pillar for the support of the head and trunk, and the vertebral foramina constitute a canal in which the spinal cord is lodged and protected. These two functions must be borne in mind when injuries to the spinal column are being treated. Between every pair of vertebræ are two intervertebral foramina, one on either side, for the transmission of the spinal nerves. The body of a vertebra is composed of spongy substance covered by a thin coating of compact bone. The vertebral arch and the processes projecting from it have thick coverings of compact bone. The body, therefore, being the weaker component, gives way first under the stress of violence. The intervertebral fibro-cartilages act as buffers, as well as being the chief bond of union between the vertebræ. The vertebræ are so firmly united to one another that injury is more likely to produce fracture or dislocation than a simple tearing of ligaments.

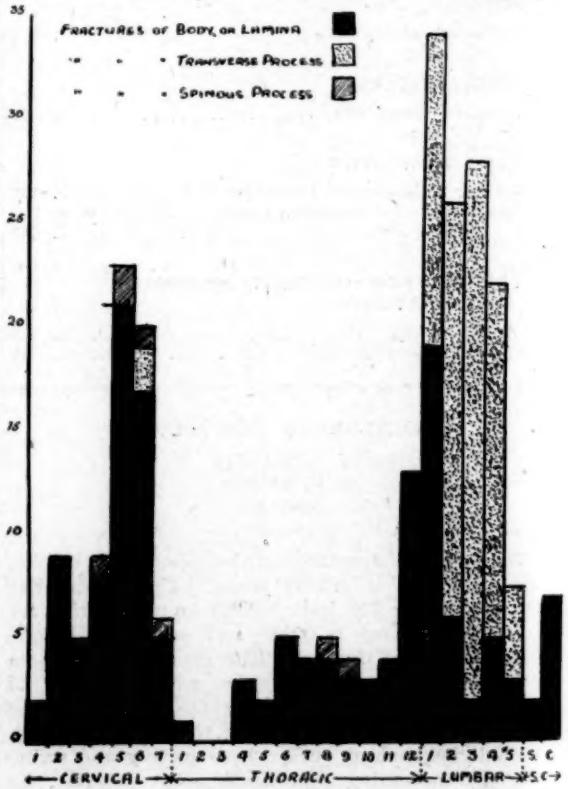
The arrangement or set of the articular processes is important. In the cervical region the superior facets look backwards and upwards, and the inferior forwards and downwards. In the thoracic region the superior facets look almost directly backwards and the inferior almost directly forwards; whilst in the lumbar region the upper facets are concave and look medially and backwards, and the lower are convex and look laterally and forwards. The capsules of the joints between the articular processes are looser in the cervical region than in the thoracic and lumbar regions. These differences explain why dislocation of the joints between the articular processes is more apt to be seen in the cervical than in the thoracic and lumbar regions, where fracture of the articular processes is more usual in severe injuries.

The cervical and lumbar regions are more mobile than the thoracic region of the spine, and therefore are more liable to suffer injury. These regions are the sites of the secondary curves which develop after birth. The cervical curve appears when the infant learns to sit up and to hold his head erect; the lumbar curve appears when the child begins to walk. The intervertebral disks are proportionately thick in the cervical and lumbar regions, and serve to increase the mobility of these regions.

The greatest number of severe injuries of the spine occur in the lower cervical region and at the junction of the thoracic and lumbar regions, that is, where the less mobile thoracic portion of the spine merges into the more mobile cervical and lumbar regions. These two sites correspond respectively to the position of the cervical and lumbar intumescences of the cord. In fracture-dislocations the upper segment is driven forwards on the lower, and the spinal medulla is compressed between the body of the vertebra immediately below and the arch of the vertebra immediately above the injury. Since the spinal medulla ends at the level of the upper border of the second lumbar vertebra, it follows that fracture-dislocations below this level, which may involve the *cauda equina*, are less serious than those above it. The subarachnoid cavity ends at the upper border of the second sacral vertebra.

Fractures of the spine are due to direct or indirect violence or to muscular action. Those due to direct violence, such as blows, gunshot wounds and other penetrating wounds, are not common in civil life. Those due to indirect violence comprise the great majority of severe spinal injuries, while muscular violence accounts for some of the minor fractures.

In order to ascertain the relative frequency and the nature of fractures of the spine treated in a large general hospital, the records of the Royal Prince Alfred Hospital were investigated. With regard to the frequency as compared with other fractures, it was found that during the three years 1934 to 1936, 933 patients with fractures were admitted to the wards for treatment, and of these, 37, or approximately 4%, had fractures of the spine. The histories of all the patients with fractures of the spine admitted to the hospital from 1910 to 1936 were examined and tabulated. There were altogether 245 fractures in 177 patients, some of whom had multiple fractures. The distribution of these fractures has been drawn up in the form of a graph.



VERTEBRA AFFECTED

GRAPH A.

In this graph (A), solid black represents fractures of the body, including the vertebral arch; the dotted areas represent fractures of the transverse pro-

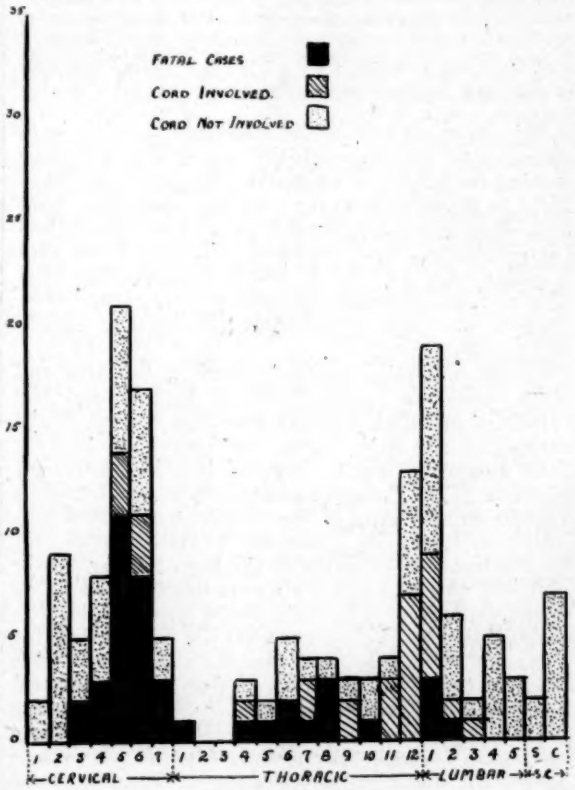
cesses; and the shaded portions, fractures of the spinous processes.

It will be noted that the greatest number of fractures of the bodies occurred at the fifth and sixth cervical vertebræ and at the twelfth thoracic and first lumbar vertebræ, that fractures of the transverse processes are confined almost entirely to the lumbar region and are relatively frequent, and that fractures of the spinous processes occur in the cervical and thoracic regions and are not common. If the sixth cervical vertebra is taken as an example, it will be seen that there were seventeen fractures of the body, two of the transverse processes, and one of the spinous process. There were nineteen fractures of the body of the first lumbar vertebra and fifteen of its transverse processes. There were two fractures of the sacrum and seven of the coccyx, and so on. Owing to lack of opportunity for X ray examination or to absence of clinical data, it was impossible to classify about thirty other cases. When there were two or more fractures, each was classified according to the vertebra or part of the vertebra affected; for example, if the bodies of the fifth and sixth cervical vertebræ were both fractured, each was counted as a separate fracture; if there was a fracture of a transverse process as well, it was counted separately. Fractures of the vertebral arches are included with fractures of the corresponding body.

A second graph (B) was prepared to show the distribution of fractures of the bodies, including the vertebral arches, and at the same time to indicate the incidence of cord involvement and the proportion of deaths. The total number of fractures of the body was 153; in 72 of these the cord was involved; 41 deaths were recorded while the patients were in hospital. In the graph each column indicates the number of fractures of the corresponding vertebral body. The black and the shaded portions together give the number of fractures with cord involvement, and the black alone gives the number of deaths. If the fifth cervical vertebra is taken as an example, it will be seen that there were 21 fractures, in 14 of which the cord was involved and in 11 of which there was a fatal termination. The body of the first lumbar vertebra was fractured 19 times, the cord being involved in nine cases and death occurring in three. It should be emphasized that a larger number of deaths occurred than are shown here, as only the deaths occurring in the Royal Prince Alfred Hospital were recorded. Here again, owing to the absence of sufficient information, in about 30 fatal cases it was not possible to indicate the level of the fracture, and these are not included in the graph. In such cases death appears to have resulted from complete lesions of the cord caused by fracture-dislocations of the cervical vertebræ, whether other injuries had been sustained or not. In fractures of the twelfth thoracic and first lumbar area a large proportion of the patients with cord involvement probably died after their transfer from the Royal Prince Alfred Hospital. Several such patients were transferred in a hopeless condition.

If these reservations are kept in mind, and if the nine fractures of the sacrum and coccyx are deducted, it will be noted that approximately 50% of the patients with fractures of the vertebral bodies suffered damage of the cord, and that of these, 57% died in the Royal Prince Alfred Hospital.

A striking observation was the infrequency of injuries to the spinal nerves at the point where they emerge from the intervertebral foramina. Mention of their involvement may have been omitted from the histories, but even if we make allowance for this, spinal nerve damage is apparently not a common accompaniment of vertebral fractures.



GRAPH B.

Having made a general survey of the 245 patients with fractures who were admitted to the Royal Prince Alfred Hospital, I shall now mention some interesting information gleaned during a perusal of the clinical histories, and at the same time I shall refer to some patients treated privately.

The graphs show that there were two fractures of the atlas and nine of the axis, but in none was the cord involved. The cause of the injury was usually a fall downstairs or from a horse, and in one case the injury was the result of the patient's diving onto another swimmer. The notes of two of the more severe cases will serve as examples.

In one instance, after the patient had fallen downstairs, there was a complaint of stiffness and pain in the neck. A radiograph revealed forward dislocation of the atlas on the axis, separation of the odontoid process, and fracture of the left side of the body of the axis and the corresponding pedicle and articular facets. There were no signs of neural damage. The patient wore for three months a plaster jacket with a collar, with favourable results.

In the second patient, a man aged thirty-one years, whom I saw privately, the injury resulted from an aeroplane accident seven weeks before. He was unconscious for two weeks. After a month in bed he was allowed up, and was informed that while he was unconscious he had got out of bed and walked several times. The thumb and fingers of the right hand were painful, numb and cold, and gave him "more trouble than anything else". The thumb and the index and middle fingers recovered after a month, but the fourth and fifth fingers were still affected. Movements of the neck, especially rotation, were restricted. An X ray examination revealed separation of the odontoid process and a fracture of the left side of the body of the axis, and a slight displacement forwards and to the right of the atlas together with the odontoid process.

This case illustrates the combination of a head and spinal injury, and the possibility of overlooking the latter. Fortunately, the patient suffered little or no harm from the oversight, but there must have been considerable risk of sudden death had further displacement occurred. He was fitted with a collar support. It is worth remembering that displacement of upper cervical vertebræ can sometimes be detected by examining the posterior wall of the pharynx.

Of the remaining cervical vertebræ, the fifth and sixth were the most liable to injury, and the incidence of neural damage was high. Many of the severe injuries at a higher level would be rapidly fatal and would not be included in this survey; for example, if the cord was completely crushed in fractures above the level of the fourth cervical vertebra, death would rapidly ensue and the victims would not be admitted to the wards of the hospital. As I have stated, a number of patients were admitted who died before a correct diagnosis or X ray examination could be made; these cases were not included in the figures. The graphs, therefore, do not give a correct idea of the incidence of fractures in the cervical region. Only two examples of fractures of the transverse processes were recorded, and five of the spinous processes. Diving into shallow water and motor car accidents were common causes of these fractures in the cervical region. There were two unusual causes; in one the victim, a nurse, turned her head suddenly to speak to another person. She felt a sudden severe pain in her neck, and X ray examination showed an incomplete lipping fracture of the body of the fourth cervical vertebra. In another instance, the spinous process of the sixth cervical vertebra was fractured while the victim was driving at golf.

As in the upper cervical region, we find examples of head injury combined with injuries at the level of the fifth and sixth cervical vertebræ. In one instance there was paralysis of the left side of the face and of the left arm and leg. The bodies of the fourth and fifth cervical vertebræ were fractured, but the paralytic symptoms were obviously due to cerebral injury and not to cord damage. In another instance, when injury of the head as the result of a motor car accident was suspected, an X ray examination of the skull was made and revealed no abnormality. As there was a complaint of stiffness and pain in the neck, a further X ray examination was made five days later. It revealed fractures of the bodies of the fourth and fifth cervical vertebræ.

When a person is rescued after suffering an injury to the neck from diving into shallow water, it should be remembered that the vigorous application of first-aid may cause further displacement of any fracture, and damage the cord, which might otherwise have escaped. This may have happened in at least one case in which there was a fracture-dislocation at the level of the fifth and sixth cervical vertebræ.

In the records there is an account of one patient who had a fracture-dislocation at the level of the fifth and sixth cervical vertebræ, but without signs of cord injury, and in whom, after the fracture had been reduced under general anæsthesia, the evidence of a complete transverse lesion appeared, with death following in forty-eight hours.

These instances indicate that any person in whom an injury of the spine is suspected should be moved and manipulated with the greatest care.

The possibility of confusion being caused by symptoms of functional nervous disorder should be remembered. An illustration of this occurrence was found in this series of cases.

A patient with a fracture of the body of the fifth cervical vertebra, in which the cord had escaped injury, developed, six weeks after the accident, anæsthesia of glove distribution up to the elbows, and weakness of the hands and forearms. These symptoms were functional and subsided with appropriate treatment.

Of patients suffering from fractures of the cervical vertebræ, only one was subjected to the operation of laminectomy. This patient had a comminuted fracture of the fourth, fifth and sixth cervical vertebræ with associated quadriplegia. Death occurred on the fourth day after the operation. The patient's friends usually clamour for something surgical to be done; but it has been my experience that laminectomy, when there is evidence of a complete transverse lesion of the cord, never benefits the sufferer.

Fractures of the thoracic vertebræ (numbers one to eleven) are comparatively infrequent, but the incidence of cord injury is high. In the 28 cases in this series there were 17 with cord injury, that is, a little over 60%. One patient fell from a horizontal bar while exercising, and sustained a fracture-dislocation of the eighth thoracic vertebra with a complete transverse lesion of the cord. He died some time later.

The brief history of a female patient who recovered may be of interest.

On June 4, 1929, as the result of a motor car accident, she sustained a fracture of the fourth and fifth thoracic vertebræ; she walked immediately after the accident,

collapsed, then recovered and walked again. When examined in the Royal Prince Alfred Hospital thirteen days after the accident, she showed loss of power in the legs and impairment of sensation. Sphincter control was defective, but was recovering. The patient had been able to tell for the previous two days when the bladder was full, and had succeeded in passing urine once. Recovery was gradual, and at the end of December of the same year the patient was able to walk.

Pathological conditions affecting the vertebræ, for example, new growths, spondylitis, tuberculosis, hydatid disease *et cetera*, may influence the site and render lesser degrees of violence effective in producing fractures.

The history of a patient, a man aged thirty-four years, who had a kyphotic spine due to spondylitis, and who suffered a fracture, may be of interest.

He was thrown from a sulky and somersaulted onto his head and shoulders. He was dazed, but got up, and as he walked he felt a grating sensation between his scapulæ. He was taken home sitting up in a motor car, and walked into the house and went to bed. His doctor saw him, but could discover no evidence of paralysis. Soon after the doctor's departure there was a sensation of pins and needles in the legs, followed by loss of power and the rapid appearance of all the signs of a complete cord lesion at the level of the fourth thoracic segment. The site of the fracture may have been determined by the pathological condition of the spine. The placing of the patient in a soft, sagging bed probably allowed the fracture to become displaced sufficiently to compress the cord. Pneumonia supervened and death occurred on the tenth day.

Fractures of the twelfth thoracic and the first lumbar vertebræ should be considered together, as fracture dislocations of the one or the other are relatively common and neural damage is a frequent complication.

It will be noted from the graph that there were few deaths from this type of fracture while the patients were in the Royal Prince Alfred Hospital. Some of the patients with cord injury at this level survive for years, but most of them ultimately succumb, the cause usually being bladder infection and pyelonephritis. This region is also important because it is the common site of those wedge-shaped crush fractures of the body which may be overlooked, and which may cause great and permanent disability. Sometimes the body is only slightly damaged, but if the patient persists in going about gradual absorption occurs and deformity increases until all the features of the condition described by Kümmell are reproduced.

One man, after a motor car accident, was admitted to a hospital and was discharged after a few days. He could walk well, but had pain in the lumbar region. He then consulted his own doctor, and it was discovered after an X ray examination that the first lumbar vertebra had been crushed. A plaster jacket with hyperextension corrected the deformity.

A young man, aged thirty years, had been thrown from a horse nine weeks previously. He felt severe pain in his lumbar region and could not get up. He was carried home and remained in bed ten days. The pain subsided in two days. He sat up for a further ten days. His back felt weak, but improved each day. After five weeks he resumed light work, but at the end of the day his back felt tired and weak. X ray examination revealed a typical wedge-shaped compression fracture of the first lumbar vertebra. The patient was fitted with a Taylor brace.

The operation of laminectomy was performed on only a few occasions, but in no case, when there was evidence of a complete lesion of the cord, was any benefit noted. The correct employment of modern methods of reduction in crush fractures and fracture-dislocations will do with few exceptions all that is necessary to relieve the cord of pressure.

Fractures of the transverse processes were very common in the lumbar region as indicated in graph "A", but there was no instance of fracture of a spinous process. Fractures of the transverse processes, while often due to direct violence, were frequently due to muscular action alone. In one case a game of leap-frog was the cause, but the history did not say which of the two participants was the victim. These fractures cause pain if the victim continues to move about. An X ray examination will reveal its cause. Fracture dislocations below the level of the first lumbar vertebra may involve the *cauda equina*.

There is little to say about fractures of the sacrum and coccyx. Only two fractures of the sacrum were noted, and they were not of consequence. Probably a number of these fractures were classified as fractures of the pelvis. Fractures of the coccyx were usually due to falls in a sitting position. They were notable because of the persistent neuralgic pain or coccydynia which often resulted. Some of these patients were admitted to hospital for excision of the coccyx.

In cases of spinal fracture, treatment should begin at the place where the accident occurs. The patient should not be allowed to stand up, to sit up, or even to move himself. He should not be lifted or carried in such a way as to flex his spine. If the site of the injury is thought to be in the cervical region he should be transferred on his back with his neck extended over a small pillow. If the injury is lower in the spine, he should be carried in the prone position. If a portable X ray apparatus is not available, the patient, if his condition permits, should be taken first to the X ray department and then to the ward. It is absolutely necessary that lateral as well as antero-posterior photographs should be taken.

The method of management of the various types of fracture will be presented by Dr. Glissan, but I shall briefly discuss some of the problems of treatment peculiar to fracture-dislocations when there is cord involvement. In addition to the usual nursing care of any very sick and helpless patient, three special difficulties must be faced when the spinal cord is damaged, namely, management of the bladder, management of the bowel, and prevention of bed sores.

Active treatment of the bladder should be instituted at once, and as infection is inevitable, measures should be taken to minimize it. These measures consist of intermittent or preferably continuous catherization, of irrigations of the bladder

with antiseptic fluids (oxycyanide of mercury solution, 1 in 4,000; saturated solution of boric acid; silver nitrate solution, 1 in 2,000; potassium permanganate solution, 1 in 2,000), of the administration of urinary acidifiers (acid sodium phosphate, mandelic acid or ammonium benzoate) and of urinary antiseptics, though the last mentioned are of doubtful value. When severe and intractable cystitis is present, suprapubic drainage is indicated.

The bowel should be carefully attended to and distension controlled. Suitable aperients and enemata are prescribed. Sometimes the use of "Pitressin" and the passage of a rectal tube will remove flatus.

The prevention of bed sores requires unremitting care of the skin by the nurses. A water bed, air bed or latex mattress should be substituted for the ordinary mattress, and it is a great advantage if one section is removable, to facilitate the placing of the bed pan. The sites which require most attention are the sacrum and heels, but any bony prominences which are subjected to pressure should be watched. In patients with cervical fractures treated by continuous extension bed sores may appear over the scapulæ.

Acknowledgement.

In conclusion, I wish to thank Dr. S. H. Lovell for his valuable assistance in the preparation of this paper. It was owing to him that the records of the Royal Prince Alfred Hospital were analysed and the excellent graphs prepared.

TREATMENT OF SPINAL FRACTURES.[1]

By D. J. GLISSAN,
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THE problem of the treatment of patients suffering from spinal fractures is approached along the same path as that leading to the correct management and care of all broken living bones. We have as our guides along this path the basic principles of reduction of the fracture, of efficient immobilization of the damaged area, and of the initiation at the earliest possible moment of active movements and intrinsic control of the muscles and joints of the uninjured and injured parts. These, if correctly applied, will lead us to the goal of restoration of the optimum degree of function and of physical and mental rehabilitation.

This last factor is of special significance in the subject at issue, since there is a paramount need to establish a high morale, to lay early and effectually the bogy of a "broken back", and to inculcate confidence and cooperation in all phases of treatment in these cases.

The means by which these principles may be followed and these ends attained have been placed by the clear and concise writings of Watson Jones within the reach of every practitioner of medicine; and I propose to do no more than summarize for you the main points of his teaching.

Since the majority of fractures of the spine are of the crush type, being due to forcible flexion of the column, the most efficient degree of reduction is obtained by fully hyperextending the affected region of the trunk. The success of this manœuvre and the ease of its application depend upon the integrity of the anterior longitudinal ligament and of those fibres of the intervertebral disks which attach the upper and lower rims of contiguous vertebræ, and upon the completeness with which the segments of the spine, proximal and distal to the site of fracture, can be controlled to furnish favourable leverage, operating upon the fulcrum opposite the fractured bone.

This last factor varies in the different regions of the column according to the degree of antero-posterior mobility which is peculiar to each. This mobility is greatest in the lumbar and cervical, and least in the dorsal region, so that the method of carrying out the necessary manipulation will vary slightly in each region. The method of dealing with a fracture of one of the lumbar vertebræ will first be described.

The patient, clothed in two seamless, sleeved, long and closely fitting cotton singlets, applied smoothly and secured front to back by a safety pin between the legs, is laid face downward with his upper and lower limbs resting on suitably placed tables and the trunk unsupported in the intervening gap. The table supporting the upper limbs should be at a higher level, to the extent of from six to eighteen inches, than that beneath the thighs.

A layer of latex rubber, or failing this, a firmly folded blanket, is placed beneath the front of the thighs, and a similar pad is provided to allow the arms folded above the head to rest on and grasp the upper support. A strip of latex half an inch thick and two to three inches wide is laid along the line of the spinous processes.

Since the active cooperation of the patient is essential, a general anæsthetic is not feasible, whilst local anæsthesia is quite unavailing to relieve the chief discomfort, which is felt beneath the supporting upper limbs and in front of the overstretched trunk. I have found that a quiet talk with the patient, explaining the procedure, inviting his cooperation, and showing appreciation of his difficulties, will ensure a most helpful and courageous response, and incidentally will lay the foundation of that control of morale which is so essential.

It need hardly be emphasized that every requirement must be ready to the surgeon's hand, and that there must be no delay, once the patient is prepared, in proceeding to the practice of the next principle of immobilization.

A start being made at the level of the intertrochanteric line, a plaster cast is rapidly applied by a series of creasless, evenly laid circular turns of plaster bandage, which must extend as high as

[1] Read at a meeting of the New South Wales Branch of the British Medical Association on May 27, 1937.

the clavicles in front. Each fresh bandage must commence where the preceeding one ends to ensure even thickness and weight. The cast must be carefully moulded about the pelvis and must be made to fit snugly against the latex pad which guards the spinous processes.

In the upper dorsal region, owing to the rigidity of this section of the spine, and in order to localize the fulcrum in the neighbourhood of the crushed body, Watson Jones modifies this technique by applying a firm calico bandage looped over the back just below the site of the fracture and secured to the floor or to the lower rung of a table at a point opposite the patient's head. The hyperextending force is applied, not by allowing the trunk to sag unsupported, but by forcing the dorsal spine backwards by means of a body sling which, supporting the lumbar region, levers the upper part of the trunk backwards against the fulcrum of the bandage loop. The plaster cast is then applied as just described.

Whilst my experience in dealing with these fractures is limited, I should be very inclined to modify this procedure by applying a cast from below the hip joints to the level of the fractured body, with the lumbar region in the position of normal extension, before applying a hyperextension force. This would then of necessity be centred over the site of fracture, and the plaster could be completed and the hip joints subsequently freed. Such a method would require care in its application to avoid the onset of pressure sores at the site of leverage at the upper level of the initial portion of the cast.

When the cervical region is affected, the same principle of hyperextension is carried out. The trunk is supported in the recumbent position on a table, to the head end of which is fixed a long, narrow, firm piece of wood; this serves to support the upper part of the thorax, leaving the neck unsupported and allowing the head to drop backwards, so extending the neck and opening up the collapsed vertebræ. The head is steadied to prevent rotation or side bending. This arrangement permits of the unhampered application of the plaster to the head and neck and the upper part of the thorax.

When the cast is completed and the plaster set, the patient is immediately lifted onto a table and the plaster is trimmed to permit of the full range of movements of the upper and lower limbs. The patient is then placed on his back on a bed furnished with fracture boards, and the cast is supported by suitably placed pillows.

Certain adverse sequelæ which may cause anxiety are liable to follow the application of any rigid casing about the body. The most noteworthy of these is vomiting, which may be an early indication of the onset of paralytic ileus or acute dilatation of the stomach. Any persistent vomiting should not, therefore, be lightly regarded. To wash out the stomach early in such cases may save much anxiety and avoid the necessity of removing the cast. The stomach should not be more than very lightly loaded for a few days, aspirin should be used instead of morphine to relieve any pain, and in certain cases a bromide mixture is of great value. Frequent change of position also may be helpful.

When the plaster is dry, those patients who have escaped spinal cord or *cauda equina* damage should be encouraged to exercise the upper and lower limbs and the spinal muscles. Deep breathing should be practised, and after a week they may be allowed out of bed to wear their ordinary clothing and to resume walking and minor routine activity.

The plaster should be retained for not less than four months, and after its removal the spine should be carefully examined, clinically and radiographically, to detect any evidence of collapse in a body or bodies which may not have become fully organized.

After a period of a month, if no adverse signs appear, the ordinary active movements of the spine may be practised as a routine, and at the earliest opportunity the patient should be instructed to swim. I know of no more useful and effective measure in the treatment of post-traumatic spinal stiffness.

There are two further matters related to the question of treatment of spinal fractures on which I should like to touch. The first concerns the so-called Kümmel's disease, and the second the transport of patients suffering from injured backs.

With regard to the former, I think it is now generally conceded that the syndrome of deformity and rigidity of the spine with which the name of Kümmel has been associated represents in effect the late result of undetected and untreated crush fractures of the spine. It is well, therefore, to examine with great care all patients whose vertebral columns have been subjected to any force likely to produce any sudden and more than ordinary flexion. Unless the whole column is examined radiologically in the two planes and the skiagrams are very carefully studied in such cases, it is possible for a crushed vertebra to escape detection, until renewed bodily activity and the superjacent weight of the trunk above the site of injury produce changes which cannot fail to be noticed.

In addition to gross structural damage to the bone architecture of one or more vertebræ, there may result from a flexion injury a type of damage which is more molecular in character. This would not be discernible in routine radiographic examination, but it would be followed by softening of the bone and a slow collapse of the affected vertebræ. This last contingency suggests that whenever the spine has been subjected to any injury of a type competent to cause a crush fracture, the question of providing some form of spinal support, even in the absence of radiographic evidence of crushing, should be very carefully weighed.

Following the writings of Watson Jones, and largely owing to his advocacy, it has been urged that during the period of first-aid and of transport, all patients whose spines have been fractured should be kept in the prone position. Whilst on the face of it this would appear to be a perfectly sound piece

of advice, a little reflection will show that to promulgate an order of this kind amongst ambulance and first-aid workers might be fraught with grave possibilities of injustice and misunderstanding.

Unless every severely injured person is transported in the prone position, it is inevitable that the bulk of patients suffering from spinal fracture will be carried in the ordinary recumbent position; for in the absence of signs of severe paralysis of the limbs or of gross deformity of the spine it is not possible for even a fully trained observer to detect spinal fractures under the conditions usually associated with first-aid. Whether it is advisable to carry all patients in the prone position is a matter for some consideration, but it has to be remembered that, in the presence of cervical fracture, transport in this position might be fraught with very serious danger.

If all ambulance and first-aid workers could be instructed to posture and carry in a suitable position all patients known to have sustained a fracture of the spine, or in whom paralysis of the limbs is obvious, then the risk of throwing too grave a responsibility on a fine body of men would be largely mitigated.

THE FUNCTIONAL PATHOLOGY OF ANÆMIA. III: RESTORATION, COMPENSATION, TOLERANCE AND FAILURE.[1]

By C. G. LAMBIE.

(From the Department of Medicine, University of Sydney.)

INTRODUCTION.

IN studying any pathological condition, we may consider (i) the immediate effects of the disease, (ii) the reaction and readaptation of the organism, and (iii) the process of failure. The immediate effect of anæmia, as we have seen, is to cause an impairment of the oxygen carrying power and carbon dioxide carrying power of the blood. It now remains to follow the second and third phases of the condition.

The reaction of the organism may be manifested in three ways: (*a*) by changes which result in the restoration of the normal state; (*b*) by the action of compensatory mechanisms, whereby the constancy of the internal environment is maintained; (*c*) by the acquisition of tolerance towards the changed condition of the internal environment when compensation is inadequate.

RESTORATION.

Blood Regeneration.

The most obvious means by which the organism can remove the anæmic state is by the regeneration of blood. This is seen in its simplest form after hæmorrhage. Whatever factors may be involved at each step in the process of blood regeneration, the condition common to all forms of anæmia, and which acts as a specific stimulus to the bone marrow, is the low tissue oxygen tension. That a low oxygen tension in the tissues can act in this way is seen in adaptation to high altitudes[3] and has been observed experimentally (Campbell[2]) in animals kept in atmospheres deficient in oxygen. The converse condition of blood formation occurs as a result of exposure to high oxygen pressures.[1][2][4] Unless the disease causing the anæmia destroys the blood, inhibits the activity of the bone marrow or deprives the body of some essential constituent for blood formation, anæmia tends to be a self-limiting disorder.

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COMPENSATION.

Utilization of Oxygen Reserve.

Although the using up of the oxygen reserve is an immediate effect of anæmia, the existence of this reserve provides a compensatory mechanism, and indeed the first line of defence against oxygen lack. It has already been sufficiently dealt with in Part I.

Lowering of Metabolism.

In 1872, Bauer[1] reported that withdrawal of 20% to 28% of the calculated blood volume in dogs was followed by a 36% diminution in the oxygen consumption and a 22% diminution in the carbon dioxide production on the day after the bleeding. As a result of these experiments the view became prevalent that lack of hæmoglobin impaired the oxidative processes and lowered metabolism. If this lowering of metabolism went parallel with the diminution in hæmoglobin, it might have some claim to be regarded as an adaptation—the demand for oxygen diminishing with the supply—provided that the lowered metabolism itself produced no harmful effects. The observations of subsequent observers have not, however, entirely confirmed those of Bauer, and have given rise to a diversity of results. Thus Finkler[3] (1875) and Pembrey and Gürber[7] (1894) have found the respiratory metabolism after bleeding to be diminished; Delchef[2] (1905) found it normal or slightly diminished. Frédéricq[4] (1885), measuring the heat production by means of the D'Arsonval compensation calorimeter, found it transiently diminished and then elevated, but his results are practically normal when the experimental error is taken into consideration. Lukjanow[6] (1884) observed a 10% increase in

[1] Parts I and II of this paper were published in the issues of August 21 and 28, 1937, respectively; Part IV is to follow.

oxygen absorption immediately after bleeding, but this did not persist on the following day. Hári[5] (1909), using a Rubner calorimeter, found the heat production increased after bleeding in one experiment on a dog, but during the period of recovery the elevation was so slight as to fall within the normal limits. The general result of these experiments appears to be that the metabolism is not greatly altered by post-hæmorrhagic anæmia; but the lack of uniformity is to be ascribed largely to faulty technique, especially in regard to muscular activity, the agitation of the animals after operative procedures, food intake, and imperfect apparatus, all of which are now known to influence the results. Acute hæmorrhage cannot be said to be an ideal method for studying the effects of anæmia pure and simple. The loss of blood volume and plasma colloid, as well as corpuscles, would lead to oligæmic failure of the circulation, especially in animals with little water in their tissues, who stand dehydration badly, while the diminished blood flow through the coronary vessels might so weaken the heart as to render compensation by increased blood flow difficult. In these circumstances a fall in metabolism might easily occur. Pembrey and Gürber[7] injected saline solution to replace the fluid withdrawn and they obtained results within the normal limits. From these experiments and from what has already been said regarding the critical level at which oxygen consumption becomes impaired as a result of lowered tissue oxygen tension, it may be concluded that there is no simple parallelism between oxygen consumption and the degree of anæmia. In acute experiments any lowering of metabolism due to excessive fall in tissue oxygen tension is to be regarded as a manifestation of failure rather than a compensatory change. We shall deal later (Part IV) with the various factors which may modify the basal metabolism in anæmia.

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Specific Oxygen Capacity of Hæmoglobin.

The finding of a normal or increased metabolism in experimental and clinical anæmia has given rise to much speculation as to the method by which the body compensates for the loss of hæmoglobin. One of the earliest theories has reference to the oxygen binding capacity of hæmoglobin. The suggestion is that in anæmia compensation would take place by each gramme of hæmoglobin being able to carry a larger amount of oxygen. A controversy over this question, in which Bohr and Hüfner were the chief protagonists of two opposing schools of thought, extended over some twenty years from 1889 to 1909. Hoppe-Seyler[23] (1889) was the first to put forward the idea that hæmoglobin varied in its composition, and as a result of studies upon the differences in behaviour between oxyhæmoglobin and reduced hæmoglobin when treated with acids, he postulated the existence of two substances: arterin in the arteries and phlebin in the veins. These views were criticized and shown to be untenable by Gamgee.[21] Later, Bohr,[11][12][14] basing his views upon the apparent inconstancy which is found in the amount of oxygen bound per gramme of hæmoglobin or per gramme of iron contained in hæmoglobin, put forward the hypothesis that there existed in the blood several modifications of hæmoglobin, which he designated as α, β, γ, δ, each of which could bind a different amount of oxygen, the hæmoglobin of the blood being a mixture of these modifications, the proportions of which could vary under different conditions. He also introduced the term "specific oxygen capacity" to denote "the ratio of combined oxygen in cubic centimetres at normal temperature and pressure to the iron in grammes in a given amount of hæmoglobin formed from laked blood or a solution of hæmoglobin crystals which had been saturated with air at 15° C." He held that the specific oxygen capacity differed in different animal species, and in different individuals of the same species, and even in the same individual at different times; finally, that it changed upon the regeneration of blood following bleeding and the injection of saline solution. He therefore came to the conclusion that by means of a change in specific oxygen capacity the body could adjust its oxygen supply according to its needs. The view of Bohr received support from the experimental results of Abrahamson[1] (1893), Haldane and Lorraine Smith[22] (1894), Tobiesen[49] (1895), and Bornstein and Müller (1907). As regards pathological conditions, they appeared to be confirmed by Mohr[37] (1906), who, experimenting with dogs and calves, reported that with diminishing hæmoglobin percentage the oxygen capacity per gramme of hæmoglobin increased. Lommel[31][32] stated that the converse held in polycythæmia, in which the oxygen binding capacity of hæmoglobin could be reduced to about half the normal.

As against Bohr, Hüfner stands out as the representative of the school believing in the unity of hæmoglobin as a single sharply characterized chemical entity. As a result of careful experiments, using spectrophotometric methods, he considered that he had demonstrated by his curves and by his light extinction coefficient relations that there was a constant ratio between the iron content and oxygen absorption of the hæmoglobin of normal blood and that hæmoglobin was identical in different

animal species, existing as one substance throughout the higher animals as regards union with oxygen.[24] He, together with Küster[25] (1894) and also Pregl[40] (1905), obtained confirmative evidence of this by a study of the union between carbon monoxide and hæmoglobin; they used volumetric and gravimetric methods, which yielded results in agreement with those obtained by the spectrophotometer in respect of the constancy of the relationship between iron content and gas binding capacity of hæmoglobin. Hüfner ascribed Bohr's results to impurities, and later Aron suggested that the discrepancies between Hüfner's and Bohr's results might have been due to the formation of methæmoglobin during the lengthy procedures involved in preparing the hæmoglobin solutions, and also to the difficulty in completely ashing the blood and estimating the iron. Aron also points out that, whereas Bohr took into account the results of all his experiments, Hüfner rejected all experiments which did not show his optical constant for hæmoglobin.

Between 1909 and 1912 a series of papers appeared which seemed to give the death blow to Bohr's theories. Thus Barcroft and Roberts[4] (1909) showed that the oxygen dissociation curve of dialysed hæmoglobin was similar to that deduced by Hüfner from chemical mass action, while a study of the effects of temperature (Barcroft and King,[5] 1909) on the dissociation curve suggested that the combination between oxygen and hæmoglobin was a chemical one and therefore obeyed the law of constant proportions. Further, Barcroft and Camis[6] (1909) found that the form of the dissociation curve was influenced by the presence of salts and that the differences in the oxygen dissociation curve of different animals could be accounted for in this way, the oxygen dissociation curve of dialysed hæmoglobin being the same for different animals. Again, Bohr himself, in collaboration with Hasselbach and Krogh[13] (1904), also Barcroft and Orbeli[7] (1910), showed that the effect of acids, such as carbonic acid, in producing variations in the oxygen binding power of hæmoglobin is such as to make it unnecessary to assume changes in the specific oxygen capacity as a means of regulating the oxygen supply to the tissues. Finally, Peters (1912), using improved methods for estimating oxygen (Barcroft's differential method) and iron (titration with titanium salts), demonstrated that in solutions of hæmoglobin of ox, sheep, pig and cat, the value obtained for the ratio of oxygen to iron is essentially the same and agrees with the value required on the hypothesis that two atoms of oxygen combine with one atom of iron ($Fe + O_2 = FeO_2$) or 401 cubic centimetres of oxygen with one gramme of iron. The evidence, therefore, pointed to oxygen being attached to the iron-containing parts of the hæmoglobin molecule, as had previously been inferred by Laidlaw[29] (1904) from a study of the effect of acids upon the splitting off of the iron-containing parts of hæmoglobin (hæmatin). As regards pathological conditions, the earlier observations of Kraus, Kossler and Scholz[28] upon the blood of normal and anæmic human beings appeared to support the view of the constancy of the oxygen capacity of hæmoglobin, but their results showed considerable variations. Butterfield[17] (1909), however, employing improved spectrophotometric methods and improved chemical methods of estimating the iron content of hæmoglobin, studied the proportions in which carbon monoxide combined with hæmoglobin, and found that it was constant within the limits of experimental error. He argued from this that the same should hold for oxygen. This constancy held not only for hæmoglobin of normal human blood, but also for human hæmoglobin in polycythæmia, pernicious anæmia, chlorosis, scurvy and lymphadenoma. Masing[34] (1909) and Masing Siebeck[35] (1910), also using spectrophotometric methods, found a high degree of constancy in the ratio of oxygen to iron in the blood of birds, mammals and human beings, both normal and suffering from anæmia. Again, Morawitz and Röhmer[38] (1908), comparing the oxygen capacity with the hæmoglobin (determined colorimetrically by the Haldane-Barcroft method), found a general, although not an absolute, parallelism between the two in anæmias and polycythæmia in man, while similar results were obtained by Douglas[18] (1909) in a study of blood regeneration following repeated hæmorrhages in rabbits.

A possible source of error in correlating the hæmoglobin content of the blood with the oxygen capacity has been pointed out by Meakins and Davies[36] (1925). They found that, whereas in most diseases the hæmoglobin percentage as determined colorimetrically ran parallel with the oxygen capacity as determined by the ferricyanide method, this did not hold in anæmia. This they ascribed to the increased metabolism of the corpuscles in anæmia, which causes the rapid reoxidation of the blood or oxidation of substances in the blood, both before and after the oxygen is liberated from the hæmoglobin by the ferricyanide.

While the constancy of the specific oxygen capacity of hæmoglobin in normal blood seems to be supported by an abundance of experimental evidence, it must be admitted that the available data regarding pathological conditions are still meagre, and the possibility exists that in disease or during blood regeneration intermediate bodies may be present which are in process of being worked up into hæmoglobin, or that hæmoglobin may be changed into other products and that these modifications might involve not only the protein (globin) fraction, but also the iron-containing part of the hæmoglobin molecule, and so affect its oxygen binding capacity. Within recent years evidence has been accumulating which appears to point in this direction. Thus Schumm[42] pointed out the frequent occurrence of hæmatinæmia in various forms of hæmolytic anæmia, and this has been confirmed by Van den Bergh and Engelkes[10] (1922) and by Snapper.[44] More recently, Engelkes[19] (1928), employing accurate methods for determining oxygen

and iron, has reported that in hæmolytic processes, for example, pernicious anæmia and malaria, there is a drop in the specific oxygen capacity, whereas in cases of secondary anæmia the specific oxygen capacity is unchanged. He attributes the drop in specific oxygen capacity to intraglobular hæmatinæmia. Although he did not succeed in demonstrating this spectroscopically in pernicious anæmia, it is to be recognized that hæmatin, even in fairly strong concentrations, cannot be observed at all spectroscopically in the presence of relatively large amounts of oxyhæmoglobin. However that may be, there appears in these cases to be a substance derived from hæmoglobin, containing iron, in the red corpuscles, which does not possess the power of normal hæmoglobin to bind oxygen in its dissociated form. These results of Engelkes contradict those of Butterfield[17] and of Masing and Siebeck.[34][35] Engelkes[19] justly criticizes Butterfield's conclusions in regard to pernicious anæmia in so far as they rest on one observation on one patient. He also points out that, whereas oxygen cannot be obtained from hæmatin either by potassium ferricyanide or by the pump, in Butterfield's method the colouring matter is first reduced to hæmochromogen, after which it takes up as much carbon monoxide as an amount of hæmoglobin containing the same amount of iron (Hüfner and Küster, 1904; Pregl, 1905). Had the diminished specific oxygen capacity been due to the presence of methæmoglobin, Butterfield's results would also have been fallacious, since in his procedure the carbon monoxide absorption takes place after reduction with hydrazine, that is to say, after methæmoglobin would have been changed into reduced hæmoglobin, which combines with carbon monoxide with avidity. Masing and Siebeck's results are also open to criticism on the grounds that comparison was not made between the oxygen binding power and the iron content of every sample of blood; but the final results were obtained by comparison with two averages (iron per gramme of hæmoglobin and oxygen per gramme of hæmoglobin) obtained from varying sources, including patients as well as healthy persons. Engelkes's results are in disagreement with those of Leschke and Neufield[27] (1922), who could find no change in the specific oxygen capacity in six cases of pernicious anæmia, although in one case they found methæmoglobin.

In the meantime other evidence is being brought forward regarding the presence in blood of modified forms of hæmoglobin. Thus, Stimson and Hrubetz (1927-1928) report the appearance of a non-oxygen-bearing modification of hæmoglobin in the blood of rabbits following splenectomy[45] or partial hepatectomy[47] or the administration of nitrobenzene.[46] Marshall[33] (1932) has shown that traces of methæmoglobin may be detected spectrophotometrically in normal blood; Engelkes finds that in apparently healthy rabbits sulphæmoglobinæmia may be present, and that in cases of autotoxic sulphæmoglobinæmia the specific oxygen capacity is lowered;[9] finally, Fairley and Bromfield[20] have found a new modification of hæmoglobin in the blood plasma of patients suffering from blackwater fever, but nothing is known of its oxygen binding power. Certain forms of hæmoglobin, giving a spectrum superficially resembling that of oxyhæmoglobin, but which do not yield up their oxygen on treatment with potassium ferricyanide or *in vacuo*, have been described by Barcroft (1928) and by van Slyke, Hastings, Heidelberger and Neill (1922), who speak of "inactive hæmoglobin"; also by Arnold (1900), van Claveren (1901) and Keilin (1926), by whom the substance is variously called kathæmoglobin or parahæmatin. It is probable that some of Bohr's results may have been due to the presence of inactive hæmoglobin in his preparations, and it is also possible that under pathological conditions some such substance may be present in the blood *in vivo*. While it is understandable that changes in the hæmatin nucleus of hæmoglobin would alter the oxygen binding capacity of hæmoglobin, the possibility has to be considered that changes in the globin part of the molecule might also indirectly bring about changes in the affinity of hæmoglobin for oxygen. According to Barcroft,[8] the modern conception of the hæmoglobin complex is a dynamic one:

> Hæmoglobin is only maintained *in statu quo* as part of a mass action, which involves hæmochromogen, and hæmochromogen itself only exists in the presence of reduced hæmatin. Of these three substances, hæmoglobin, hæmochromogen and hæmatin, only one, namely hæmoglobin, contains oxygen which can be abstracted in the free state by ferricyanide or by a vacuum, whilst all three contain iron.

In normal blood the amount of hæmatin and hæmochromogen cannot be more than 2%; otherwise Peters's ratio for the volume of oxygen per gramme of iron in hæmoglobin, as corrected by Burn, would have shown greater deviations from the theoretical requirement, namely, 401 cubic centimetres. In pathological conditions, however, the diminished specific oxygen capacity found by various observers might conceivably in some instances be due to the presence of larger amounts of these substances. With regard to the possible effects of the changes in the protein of hæmoglobin, Barcroft points out that "some slight change in the nature of the globin might produce a hæmochromogen which was much less likely than that of the normal body to go completely to hæmoglobin". In that case there would be a greater proportion of hæmochromogen and hæmatin, and therefore an excess of iron in proportion to dissociable oxygen. A considerable body of evidence exists to show that the globins of different animal species differ considerably in chemical constitution and immunological properties, while Tadokora, Abe and Yoshimura[48] describe physico-chemical differences (solubility, isoelectric point, amino-acid content) between α, β, γ and δ hæmoglobin (reminiscent of Bohr's nomenclature) in normal individuals of the same species. These differences, however, usually seem to produce no significant effect on the specific oxygen capacity of hæmoglobin, but to what extent this holds for pathological conditions has not been ascertained. In this connexion it may be mentioned that Schenck[41]

(1930), as a result of the analysis of the proportions of various amino-acids in globin, comes to the conclusion that there is a juvenile form (rich in arginin) present in immature corpuscles of the newly born, and an adult type (rich in histidin and lysin), and that the former is increased in hypochromic anæmias but not in hyperchromic anæmias, in spite of the existence in the latter of immature corpuscles. Similarly, Brinkman, Wildschut and Wittermanns[116] (1933), on the basis of their measurement of the rate of denaturation of human hæmoglobin by means of alkali at pH 12 to form globin hæmochromogen, come to the conclusion that there are two kinds of hæmoglobin in normal human blood and that in children and newly born the resistant form is greater in amount than in adults. Comparing his results with those of Schenck, he suggests the possibility that there may be an original fœtal (resistant) type and an adult type of hæmoglobin. The possible bearing of these findings upon pathological conditions is obvious.

The present position may be summed up as follows: There is no evidence that the specific oxygen capacity of hæmoglobin can vary; but it has been shown that various modifications of hæmoglobin may appear in the blood, which have a specific oxygen capacity different from that of hæmoglobin itself. As these modifications of hæmoglobin have a smaller specific oxygen capacity than hæmoglobin, no support is given to the view that a compensatory increase in the specific oxygen capacity of hæmoglobin occurs in anæmia. The modified forms of hæmoglobin are the direct result of disease and enable less, not more, oxygen to be carried per unit volume of blood.

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Size of Corpuscles.

A diminution in the total number of corpuscles and in the total amount of carbonic anhydrase and hæmoglobin present in the blood might to a certain extent be compensated for by increased activity on the part of the individual corpuscles. Microcytosis, by increasing the total corpuscular surface exposed to the plasma for a given corpuscular volume, and by diminishing the distance over which molecules have to diffuse, would facilitate the interchange between corpuscles and plasma and so accelerate the total "turnover".

Concentration of Hæmoglobin and of Carbonic Anhydrase.

We have no evidence at present that the mean corpuscular hæmoglobin concentration can be increased to any significant extent by pathological conditions; in most blood diseases it remains unaltered, post-hæmorrhagic anæmia and idiopathic hypochromic anæmia being exceptions to this rule.[1][2][6][7][8][9] On the other hand, the mean corpuscular carbonic anhydrase concentration is increased in many anæmias, especially in hæmolytic anæmias (Lambie[4]). (See Figure XVI.) The effect of such an increase might be to accelerate the uptake and dissociation of carbon dioxide. The presence of a high mean corpuscular anhydrase concentration in pernicious anæmia might at first suggest that it was an adaptation to macrocytosis, since in such a condition the corpuscles would be at a disadvantage owing to the increase in their average size; but this view is rendered untenable by the finding of similar high values in the microcytic anæmia of familial hæmolytic jaundice. It is also uncertain to what extent an increase in the concentration of carbonic anhydrase would accelerate the reaction, as it is unknown whether the relationship between the concentration of enzyme and the rate of catalysis is a linear one under the conditions present in the corpuscles. In experiments *in vitro* the rate of evolution of carbon dioxide from bicarbonate solution does not increase in linear proportion to the carbonic anhydrase at high concentrations of the enzyme, because diffusion of carbon dioxide from the liquid into the gaseous phase becomes a limiting factor.

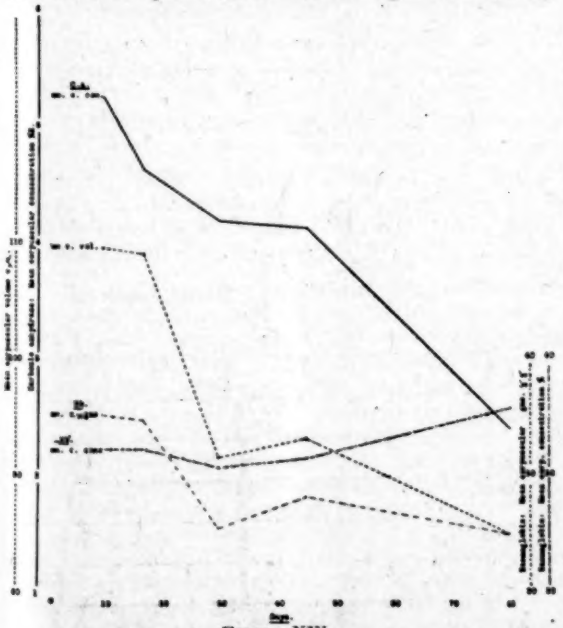

FIGURE XVI.

Showing contrast between curves of mean corpuscular carbonic anhydrase concentration expressed as *per centum E* (*E* = amount of enzyme necessary to double the rate of the reaction $CO_2 + H_2O \rightleftarrows H_2CO_3$) and mean corpuscular hæmoglobin concentration expressed as percentage in a case of pernicious anæmia. Mean corpuscular hæmoglobin is expressed in micro-microgrammes (γγ), and mean corpuscular volume as percentage.

The blood would appear to possess ample reserves of carbonic anhydrase, for whereas it requires to have only enough to accelerate the dissociation of carbon dioxide 150 times, the amount actually present, given adequate dilution, could accelerate it about 1,500 times at 38° C. In the body, however, the carbonic anhydrase, although it may be diminished in total amount in the blood,[3] does not undergo dilution in the corpuscles, except in idiopathic hypochromic anæmia and during blood regeneration after severe hæmorrhage.[4] Therefore, decreasing the amount of carbonic anhydrase in the body to a tenth of the normal value would more readily reduce the carbonic anhydrase to the minimum requirement than if it were simply diluted to this extent. If the presence of an increased concentration of enzyme does accelerate the conversion of carbon dioxide into carbonic acid at the periphery, it will also indirectly facilitate the liberation of oxygen from hæmoglobin by raising the hydrogen ion concentration in the cells. The reverse would occur in the lungs. A diminution in carbonic anhydrase concentration might have the opposite effect. It is probable, however, that the concentration of carbonic anhydrase in the corpuscles is ample in relation to the hæmoglobin content. The system carbonic anhydrase-hæmoglobin should be regarded as a unit in so far as the uptake and dissociation of carbon dioxide are concerned; and, with the possible exception of post-hæmorrhagic anæmia, in which the carbonic anhydrase-hæmoglobin ratio may be very low, neither carbonic anhydrase nor hæmoglobin can by itself be regarded as a limiting factor.

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Oxygen Dissociation Curve of Hæmoglobin.

Although, as we have seen in the discussion on specific oxygen capacity, the amount of dissociable oxygen carried per gramme of hæmoglobin, or rather modifications of hæmoglobin, or iron may be less than normal in some anæmias, there is also evidence that the affinity of the active hæmoglobin for oxygen may be diminished. This is shown by the oxygen dissociation curve of blood (Litarczek, Aubert and Cosmulesco,[6] 1929; Richards and Strauss,[10] 1926; Bansi and Groscurth,[1] 1930). Litarczek, Aubert and Cosmulesco[6] (1929), for example, have studied the oxygen dissociation curve of whole blood after hæmorrhage in rabbits, and in two cases of pernicious anæmia, in two cases of lymphatic leuchæmia, and in one case of subacute endocarditis, and find that the value of the dissociation constant k in Hill's (1910) equation[1] falls,[2][3][4] which means that there is a decrease in the affinity of hæmoglobin for oxygen. This diminished affinity of hæmoglobin for oxygen would be of value to the organism in anæmia (Litarczek, Aubert and Cosmulesco,[7] 1929), since it would mean that in spite of the diminished oxygen content of the blood, the oxygen would be given off with greater ease to the tissues for a given fall in oxygen tension. It may therefore, from this point of view, be regarded as a compensatory change. Litarczek, Aubert and Cosmulesco[8] (1929) report a linear relationship between this decreased affinity for oxygen as expressed by the reciprocal of the dissociation constant $\frac{1}{k}$ on the one hand and the utilization of the oxygen capacity as expressed by the ratio

$$\frac{\text{Basal metabolism in litres } O_2 \text{ per hour per square metre of body surface} \times 100}{\text{Oxygen capacity}}$$

on the other. (See Figure XVII.) From this, together with the fact that they could find very little change in the circulation rate, they consider that the change in the dissociation curve of oxyhæmoglobin is the chief compensatory mechanism at work in anæmia; but this conclusion is not justified, since their method of estimating the circulation rate (Liljestrand and Zander's,[5] 1928) was unreliable (see below); and in any case, with a constant oxygen consumption and circulation rate an increased utilization of the oxygen capacity would occur, even without any change in the dissociation curve of oxyhæmoglobin. Litarczek and Dinischiotu[9] (1933) correlate this diminished affinity of hæmoglobin for oxygen with alterations in the spectrum (see Figure XVIII) of oxyhæmoglobin and carboxyhæmoglobin (displacement of the α band towards the red end in the case of the former and towards the violet end in the case of the latter), as determined by means of the Hartridge reversion spectroscope, and with increase of the glutathione content of the red corpuscles. They attribute the changes in the spectrum and in the dissociation curve to the formation of compounds of hæmoglobin with glutathione. Before coming to such a conclusion, however, it would seem desirable to find out whether the changes in the dissociation curve can be related to changes either in the structure of hæmoglobin itself or to the concentration of

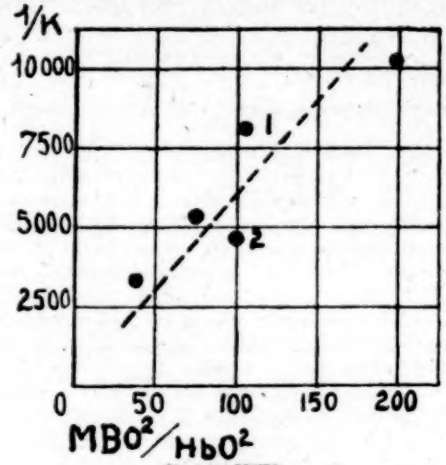

FIGURE XVII.

Curve showing the relationship between the value of the constant $\frac{1}{k}$ and the ratio between the basal metabolism in metres of oxygen per square metre of body surface (MBO^2) multiplied by 100 and the oxygen capacity (HBO^2). [After Litarczek, Aubert and Cosmulesco (*Comptes rendus des séances de la Société de biologie*, Volume CII, 1929).]

electrolytes in the corpuscles. Apart altogether from any changes in the dissociation curve of oxyhæmoglobin, the rapid reduction of hæmoglobin in anæmia causes the steep part of the dissociation

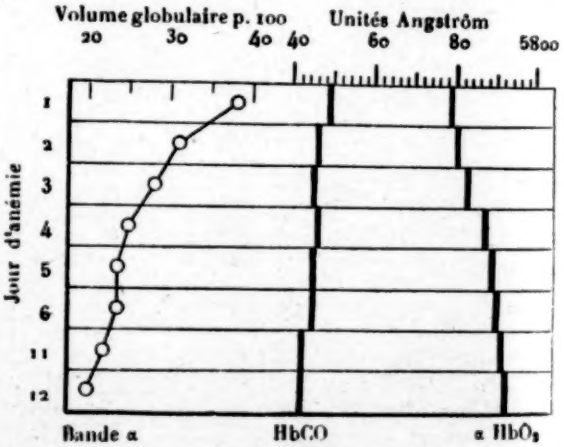

FIGURE XVIII.

Illustrating the changes in the spectrum of oxyhæmoglobin and carboxyhæmoglobin in blood at different stages of anæmia. [After Litarczek and Dinischiotu (*Comptes rendus des séances de la Société de biologie*, Volume CXII, 1933).]

curve to be encroached upon to a much greater extent than normally during the unloading of

[1] Hill's equation: $k x n = \frac{y}{100 - y}$, where x = the pressure of oxygen in millimetres of Hg; y = the percentage saturation of hæmoglobin with oxygen; 100 − y = reduced hæmoglobin; n = number of molecules of hæmoglobin. (n = 2·5.)

oxygen, which means that during this phase oxygen is given off more readily from hæmoglobin. This again constitutes an important adaptation to the changed conditions in anæmia.

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Sulphydryl Compounds: Glutathione.

That glutathione and other sulphydryl compounds might subserve the rôle of catalysts (hydrogen acceptors) in oxidative processes in cells, that is to say, oxidations of the type described by Wieland,[21][22] which consist essentially in the loss of hydrogen, has long been considered probable (Heffter,[9] Arnold,[1] and Hopkins[11][12]); but that the red corpuscles, whose intrinsic metabolism is very low, should contain considerable amounts of glutathione and other sulphydryl compounds, such as thionine (Benedict, Newton and Behre[3]) is not a little puzzling. Blanchetière, Binet and Mélon[4] reported that the amount of reduced glutathione in the corpuscles was increased in asphyxia and that the amount was greater in venous than in arterial blood. This result was confirmed by Gabbe,[6][7] who believed that the union between oxygen and the hydrogen of reduced glutathione in the lungs to form water would account for about 10% of the normal oxygen consumption. Doubt, however, has been thrown upon the importance of these findings by Litarczek, Aubert and Cosmulesco,[15] who showed that at oxygen pressures between 100 and 50 millimetres of mercury, that is to say, at tensions not much beyond the normal range (40 to 96 millimetres of mercury) in arterial and venous blood at rest and in the presence of a carbon dioxide tension approximately that of the alveolar air, the oxidation of glutathione is complete. These workers studied the dissociation curve of reduced glutathione, first of all in whole blood, by equilibrating the blood with various tensions of oxygen in much the same way as in constructing the oxygen dissociation curve of hæmoglobin, only the amount of reduced glutathione in the blood instead of the oxygen was estimated. Although at 39 millimetres of mercury carbon dioxide tension glutathione became reduced when the oxygen tension fell below 50 millimetres of mercury, lower pressures of carbon dioxide diminished the amount of reduction, while increasing the carbon dioxide tension increased the reduction for a given oxygen tension. When crystalline glutathione was dissolved in plasma, the dissociation curve was different from that obtained with whole blood, dehydrogenation being incomplete until pressures of over 100 millimetres of mercury were reached (Litarczek, Aubert, Cosmulesco and Comanesco,[17] 1931). From this the authors conclude that the presence of hæmoglobin alters the form of the dissociation curve, and that some sort of interaction takes place between glutathione and oxyhæmoglobin, whereby they mutually modify each other's dissociation curve. There does not appear, however, to be sufficient evidence to warrant this conclusion. Bansi and Rohrich[2] have confirmed the results of Litarczek, Aubert and Cosmulesco concerning the dissociation curve of reduced glutathione in respect of oxygen pressures above 50 millimetres of mercury. They find, however, that at pressures below 21·5 millimetres of

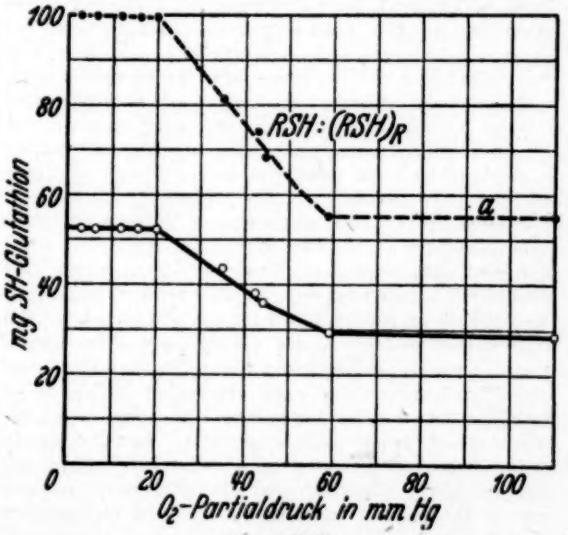

FIGURE XIX.

Showing dehydrogenation curve of reduced glutathione in blood with increasing partial pressures of oxygen in presence of a constant carbon dioxide tension of 43 millimetres of mercury. Curve *a* represents the percentage dehydrogenation at various oxygen tensions. [After Bansi and Rohrich (*Archiv für experimentelle Pathologie und Pharmakologie*, Volume CLXXVI, 1934).]

mercury all the glutathione is in the reduced form, so that it is only at oxygen pressures between 21·5 and 50 millimetres of mercury that any alteration takes place in the form of glutathione (see Figure XIX). In view of these results, they consider that glutathione enters into the respira-

tory cycle only under conditions of oxygen want when it can act as an "accessory respiratory substance" (*Atmungshilfskörper*). By studying the relationships between the total amount of glutathione and the total amount of reduced glutathione, they came to the conclusion that glutathione existed in the blood in two forms: a reversible and a non-reversible form. In anæmia and other conditions of oxygen lack the total amount of glutathione in the blood was increased, with a relative increase in the reversible form. This confirms the observations of Litarczek, Dinischiotu and Nestoresco,[14][18] who also found a total increase in the glutathione content of blood in anæmia with a relative increase in the dehydrated form. Similarly, Delrue and Vischer[5] found an increase in the glutathione in the blood at high altitudes. This increase in glutathione is regarded as affording some presumption that the substance plays a compensatory rôle under conditions of oxygen lack.

Bansi and Rohrich's[2] conception of the mode of action of glutathione is expressed as follows.

In the lungs—place of high oxygen tension—

$$4RCH_2SH + O_2 = 4RCH_2S + 2H_2O.$$

At the periphery—place of low oxygen tension:

$$2RCH_2S + H_2 = 2RCH_2SH.$$

It will be seen that in the lungs the hydrogen of glutathione interacts with oxygen to form water, while at the periphery hydrogen is taken up. It is calculated that in this way more than 15% of the oxygen consumption is accounted for in anæmia. It is difficult, however, to see how, by means of such a mechanism, glutathione could play any useful rôle as an accessory respiratory substance in the transport of oxygen, unless an amount of oxygen equivalent to that used up in the lungs to form water were liberated at the periphery. As above represented, the process seems a futile one, consisting merely in the utilization of oxygen to form water. That the process is reversible and that the possibility exists that oxygen may be formed during the process of reversal is perhaps suggested by the dissociation curve. If so, presumably this oxygen would have to come from the splitting of water, which is improbable. On the other hand, it is possible that in the lungs the hydrogen of glutathione may unite with oxygen to form a fairly stable peroxide and that with the fall of oxygen tension in the corpuscles at the periphery, oxygen may be dissociated from it. This may be represented as follows:

$$4RCH_2SH + 2O_2 = 4RCH_2S + 2H_2O_2 = 4RCH_2S + 2H_2O + O_2$$

Although hydrogen peroxide is shown in the equation, an organic peroxide could also function in the body. In the scheme suggested by Bansi and Rohrich, active hydrogen is supposed to come from the tissues, but it is difficult to see how this could occur, since the active hydrogen would not migrate from the tissues into the corpuscles where the glutathione is present. Hydrogen would have to be derived from the dehydrogenation of some substance such as lactic acid within the corpuscles. If glutathione were to play any significant rôle in the respiratory cycle, this continual dehydrogenation (oxidation) at the periphery at every round of the circulation would make it necessary to suppose that the corpuscles in anæmia have a very much higher metabolism than normally. Actually the red corpuscles do have a higher metabolism in anæmia, but the increase is dependent upon the presence of immature cells, particularly reticulocytes (Harrop,[8] 1919), so that on this hypothesis it would be only the glutathione of the immature cells which could function in anæmia. The reversibility of oxidation and reduction of glutathione under varying tensions of carbon dioxide are considered by Turner[20] to be of physiological importance. The effect of carbon dioxide may merely be to alter the conditions of pH which favour the action of catalysts concerned with hydrogenation or dehydrogenation. On the other hand, it may be that some of the hydrogen of the bicarbonate formed under the action of carbonic anhydrase from water and carbon dioxide may go to glutathione as well as to hæmoglobin, and hæmoglobin may even act as a catalyst which would convert the hydrogen into the active form:

$$CO_2 + H_2O \rightarrow H'CO'_3 \qquad Hb$$

$$\vdots$$

$$H'HCO_3 + KHbO_2 = KHCO_3 + O_2 + H$$

$$\vdots$$

$$RCH_2S$$

This, however, while facilitating the hydrogenation of glutathione, might possibly (although not necessarily) be a disadvantage from the point of view of the liberation of oxygen from hæmoglobin, as the dissociation of oxygen is facilitated by the taking up of hydrogen by hæmoglobin.

If glutathione were to play any rôle in the respiratory cycle in the blood, the time factor would have to be taken into consideration, but no evidence has been brought forward to show that the reversible reactions referred to would go forward to any significant extent within the brief period during which the blood traverses the capillaries.

Oberst and Woods[19] could find no correlation between the percentage of oxygen saturation and the percentage of reduced or oxidized glutathione in venous blood, but in view of the very long time their blood samples were allowed to stand before the estimation of glutathione was carried out, it is difficult to draw any conclusions from their results. The whole question of the importance of glutathione in the respiratory cycle and its rôle as an accessory respiratory substance in anæmia must therefore remain *sub judice*.

Finally, it is necessary to point out that the iodine method of estimating glutathione in blood, which is that used in all the investigations referred to, may be fallacious, as the other substances, such as ascorbic acid, would be titrated at the same time. This may have some bearing on Bansi and Rohrich's view of the existence of a reversible and a non-reversible form of glutathione.

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Circulatory Adjustments.

Evidences of Increased Cardiac Output.

Diminished Arterio-Venous Oxygen Difference.—It has been pointed out (Part I) that in anæmia the A-V oxygen difference becomes diminished. This observation might furnish indirect evidence of an increased cardiac output, provided that the oxygen consumption were either unchanged or increased; but we have seen that in anæmia the metabolism, in some tissues at all events, is liable under certain conditions to be diminished, even although the total oxygen consumption of the body may be normal or increased. It is, therefore, necessary to seek for some more direct means of studying the changes in the circulation.

Tachometer Readings.—Kraus[9][8] (1897, 1893) was the first to attempt to measure the blood flow in anæmia, using the tachometer, and came to the conclusion that the rate of flow was increased. He also made indirect calculations of cardiac output on the erroneous assumption that the output of the heart per beat remained constant in spite of increased pulse rate.

Direct Measurements in Animals.—Mohr[15] (1906) determined the cardiac output in experimental anæmia produced by bleeding in dogs. He employed a method depending upon the principle that if sufficient fluid is run into the circulation to maintain the blood pressure at a constant level during a temporary stoppage of the heart (by vagus stimulation), the amount run in over this period will correspond to the amount of blood the heart would have pumped out in the same time. By means of an electrical device fluid was automatically run from a burette into the central end of the carotid the moment the blood pressure began to fall during vagus stimulation. In five out of six experiments he obtained an increase in cardiac output, which in some experiments amounted to 13% to 40%. The stroke volume was also increased.

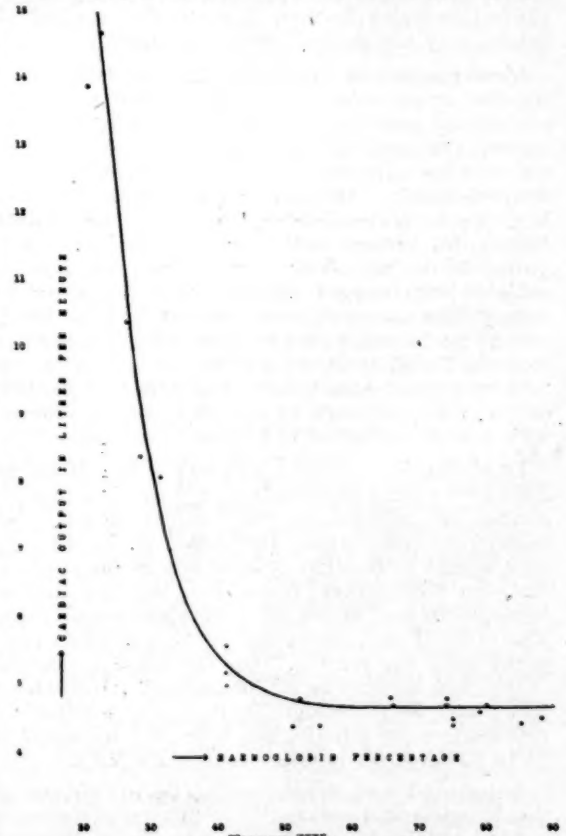

FIGURE XX.

Curve showing cardiac output in presence of various percentages of hæmoglobin. [After Dautrebande (*Comptes rendus des séances de la Société de biologie,* Volume XCIII, 1925).]

Weizacker[22] (1911) also reported that the cardiac output was increased in experimental anæmia in dogs. Blalock and Harrison[1] (1927) have, however, carried out experiments on dogs, anæmia being produced by small repeated hæmorrhages, with or without replacement by saline solution. The cardiac output was determined by the Fick[6] method, blood being obtained by puncture of the right and left ventricle in animals under morphine narcosis or in unanæsthetized trained animals. It was found that frequently no significant change in cardiac output occurred until the hæmoglobin fell below 60%, but that in many cases some increase occurred with milder degrees of anæmia. While these experiments are probably the most satisfactory that have been performed on animals, hæmorrhage is not an ideal way of studying the effect of anæmia upon the circulation, as there are too many complicating factors. More useful information might be expected from a study of the clinical anæmias in man if a suitable method of determining the cardiac output were available.

Measurements in Man.—Plesch[17][18] (1909) was the first to measure the cardiac output in anæmic patients by means of rebreathing methods. His procedure consisted in first respiring nitrogen to diminish the oxygen content of the residual air and then rebreathing the mixture in and out of a rubber bag. In normal individuals he found the cardiac output to average 4·4 litres per minute. His protocols do not show any figures for anæmic subjects with oxygen capacities corresponding to hæmoglobin values (Haldane scale) between 100% and 50%; but in patients with oxygen capacities between 5 and 10 cubic centimetres, equivalent to 22% to 50% of hæmoglobin, the estimated cardiac output varied between 10 and 20 litres per minute, with a mean output of 14·4 litres per minute.

Dautrebande[3] (1925), employing the Meakins-Davies[14] (1922) modification of the carbon dioxide method of determining the cardiac output, and taking due precautions (not observed by Plesch) with regard to the time relationship of the observations to food intake, found that so long as the hæmoglobin was above 50% (Haldane scale) there was little, if any, alteration in the output as compared with the normal. On the other hand, the output rose sharply as the hæmoglobin fell to about 40%; with 30% hæmoglobin it was approximately 8 to 9 litres per minute, and with 20% hæmoglobin 14 to 15 litres per minute (see Figure XX).

Liljestrand and Senström[11] (1925-1926), using the Krogh and Lindhard[10] (1912) nitrous oxide method, obtained somewhat similar results. Between 80% and 100% hæmoglobin (Haldane scale) the output was normal, that is to say, about four litres per minute. With the exception of one case, in which the output rose to 6·2 litres per minute, there was only a slight and doubtfully significant rise in the output as the hæmoglobin fell from 80% to 40%. Only a single case is recorded with a hæmoglobin percentage below 40; the patient had an output of 8·5 litres per minute, with a hæmoglobin value of 30%, corresponding very closely with Dautrebande's figure at the same point of his curve.

Richards and Strauss[19] (1928), employing the carbon dioxide technique described by Field, Bock, Gildea and Lathrop[7] (1924), obtained results which resemble the preceding (see Figure XXI).

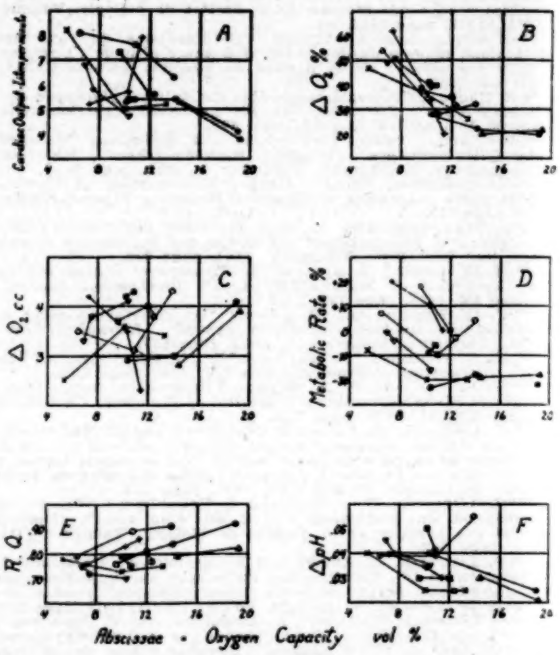

FIGURE XXI.

Curves illustrating changes in circulatory functions in anæmia. Abscissæ in each chart represent oxygen capacities in volumes *per centum*. ΔO_2 c.cm. = arterio-venous oxygen difference in cubic centimetres per 100 cubic centimetres of blood. ΔO_2 per cent. = percentage utilization of the oxygen capacity. Δ pH = difference between arterial and venous plasma pH. [After Richards and Strauss (*Journal of Clinical Investigation*, Volume V, 1928).]

When the same case was followed, a slight increase of about one litre per minute was observed as the oxygen capacity fell from 20 to 14, that is to say, as the hæmoglobin dropped from 100% to 70%, with a further slight increase in output as the hæmoglobin (again taking the equivalent of the oxygen capacity) fell to 50%. Below this level the cardiac output rose more rapidly: with 40% hæmoglobin (eight cubic centimetres oxygen capacity) it was about six to seven litres, and with 29% hæmoglobin (six cubic centimetres oxygen capacity) it was approximately eight litres—a very close agreement with the figure recorded by Dautrebande and by Liljestrand and Senström.

We may therefore conclude on the basis of experiments with rebreathing methods, that the cardiac output is definitely increased in anæmia, that this increase is very slight until the hæmoglobin falls to 50%, and that with hæmoglobin values of 30% the

output may be doubled. The very high values obtained by Plesch are to be ascribed to the inaccuracies inherent in his method; but as none of the methods employed in the above experiments is entirely satisfactory, the question requires reinvestigation by more recent methods, for example, the acetylene method. So far only one case has been studied by means of the acetylene technique[1] (Nielsen[16]). Somewhat lower figures for cardiac output have been recorded by other observers, but this is not surprising, as failure of the circulation due to oxygen lack or toxæmia may cause an inadequate response in some cases. Thus Fahr and Ronzone[5] (1922) obtained a rough estimate of the cardiac output by applying the Fick[2] principle[6] after determining the total oxygen consumption and the oxygen content of venous (direct determination) and arterial (calculated from hæmoglobin and assuming normal saturation) blood. They found that with a hæmoglobin value as low as 12·2% the output was only 10·7 litres, or 2·5 times the normal output for the patient's size and weight. Again, Blumgart, Gargill and Gilligan[2] (1931), investigating the velocity of blood flow (as distinct from the volume) through the lungs or from arm to heart (by injection of radium *C*) found that in some anæmias, for example, those due to carcinoma, the rate of flow is not as great as in others with a similar degree of anæmia.

The lowest figures for cardiac output in anæmia are those recorded by Litarczek, Aubert and Cosmulesco[13] (1929) (see Figure XXII) using the

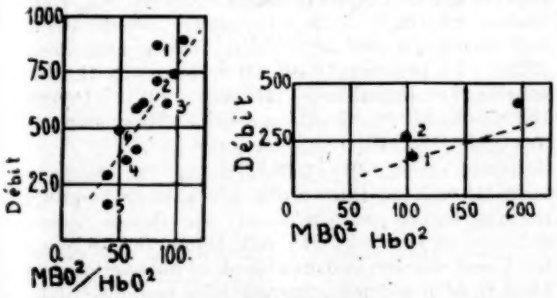

FIGURE XXII.

Charts illustrating the relation between cardiac output and the ratio between the basal metabolism in litres of oxygen per square litre of body surface (MBO^2) multiplied by 100 and the oxygen capacity (HBO^2) in anæmia (right) and in hyperthyreoidism (left).

method of Liljestrand and Zander[12] (1928). In this method the output is computed by multiplying the pulse rate by the reduced differential pressure, that is to say, the differential pressure multiplied by 100 and divided by the mean pressure, the mean pressure being defined as the average of the systolic and diastolic pressures:

$$\text{Pulse rate} \times \frac{\text{Differential pressure} \times 100}{\text{Mean pressure}}.$$

Even by this method a definite rise in cardiac output, from 2·5 litres in the normal to 4·0 to 5·0 litres in anæmia, is obtained. It is very doubtful, however, whether there is any direct relationship between pulse rate, pulse pressure and cardiac output (Schönwald,[20] 1931), especially in anæmia where, in addition to individual variation in the elasticity of the veins, the conditions are complicated by changes in the viscosity of the blood.

Stroke Volume.—Since the pulse rate is not, as a rule, markedly increased in anæmia, the increased cardiac output is achieved largely by means of an increase in the amount of blood ejected into the aorta at each systole of the left ventricle. Such an increase in stroke volume is recorded by Mohr, Plesch,[17] Dautrebande,[3] Liljestrand and Senström,[11] Richards and Strauss,[19] and Fahr and Ronzone.[5] As might be expected from Plesch's results for cardiac output, his figures for stroke volume appear excessively high; 143 cubic centimetres is given as the mean for anæmia cases, as compared with 58 to 74 cubic centimetres for normals. In one case it was nearly 200 cubic centimetres, or about the limit of the capacity of the left ventricle. Fahr and Ronzone also obtained a high value for stroke volume (140 cubic centimetres), while the lowest figures are those of Richards and Strauss. As among normal persons, there are great individual variations in the method by which increased cardiac output is achieved, depending upon the efficiency of the heart muscle.

Advantages of Increased Cardiac Output.

The advantages of increased blood flow in anæmia are obvious. It serves to compensate for the diminished oxygen carrying power of the blood by enabling the same blood to be used oftener; although each unit volume of blood carries less oxygen, the increased amount of blood flowing through the tissues maintains the oxygen supply per minute. The dilatation of capillaries in the more active organs which accompanies the increased flow, facilitates the diffusion of oxygen throughout the tissues supplied, and diminishes the oxygen tension difference between the tissues in the blood and between the arterial and venous blood. The diminished arterio-venous oxygen difference results in raising the average capillary oxygen tension, and this in turn leads to a rise in the tissue oxygen tension. If compensation were complete, the tissue oxygen tension would be normal, but this does not always occur (Campbell[3]). The importance of the increased flow is not that it should raise the tissue oxygen tension to the normal, but that it serves to keep the tension above the critical level at which tissue respiration becomes impaired.

Increased cardiac output would likewise compensate for diminished carbon dioxide carrying

[1] Since this was written a paper has appeared in the *Journal of Clinical Investigation* (Volume XVI, 1937, page 431)[21] by Stewart, Crane and Dietrick, recording determinations of the cardiac output in anæmia by means of the acetylene method. Their results confirm those of previous investigators in regard to the increase in cardiac output.

[2] $\frac{\text{c.cm. of oxygen consumed per minute}}{\text{c.cm. of oxygen taken up per unit volume of blood passing through the tissues}}$ = c.cm. of blood passing through lungs per minute.

power of the blood, by supplying the tissues with more blood for the uptake, transport and elimination of carbon dioxide. Although the "turnover" of carbon dioxide may be less per unit volume of blood, the total carbon dioxide "turnover" may be brought up to normal. In this way sufficient carbon dioxide may be removed to prevent a rise of carbon dioxide tension in the tissues at rest. The arteriovenous pH difference would also become less than it would otherwise be.

The increased cardiac output has two other effects. It is part of the mechanism for maintaining the blood pressure in the presence of diminished blood viscosity. It would also serve to prevent the accumulation of noxious metabolites which are apt to appear in the tissues in the presence of oxygen lack, for example, those which cause pain and peripheral fatigue.

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Causes of Increased Cardiac Output.

Mechanical Factors.—The mechanical factors to be considered are: changes in blood volume, and in the specific gravity and diminished viscosity of the blood.

1. Changes in Blood Volume.—An increase in blood volume, by increasing the amount of blood returning to the right side of the heart, would lead to increased cardiac output. Lorrain Smith[12] (1900), using the carbon monoxide method of Haldane and Lorrain Smith[7] (1900), found the total blood volume enormously increased in chlorosis. Plesch[11] (1909), using a similar method, confirmed this, but reported that in pernicious anæmia and in the anæmia of hepatic cirrhosis the blood volume was diminished. The accuracy of the carbon monoxide method has, however, been called in question (Gulland and Goodall,[6] 1914; Dryer, Ray and Ainley Walker,[4] 1913) in view of the absorption of carbon monoxide by extravascular hæmoglobin and the disturbance of the ratio between intravascular and extravascular hæmoglobin which occurs in many blood diseases.

Owing to the existence of such fallacies, attempts have been made to study the blood volume in anæmia by various dye methods. These have confirmed the existence of an increased blood volume in chlorosis, and it has been shown that an increase also occurs in ankylostomiasis (Boycott[2]), Banti's disease (Keith,[9] 1923—vital red), splenic anæmia, and Gaucher's disease (Giffin, Brown and Roth,[5] 1929). In practically all other anæmias the blood volume is diminished (Bock,[1] 1921; Denny,[3] 1921; Keith,[9] 1923; Keith, Rowntree and Geraghty,[8] 1915).

Menderhausen[10] (1923), using the congo red method, reports that the blood volume is roughly parallel to the red cell count; but this is certainly not always the case. In post-hæmorrhagic anæmia the blood volume is diminished in proportion to the amount of blood lost, the vascular response and the amount of fluid available in the tissues to replace that which has been removed.

We may, therefore, conclude that, with few exceptions, increase of blood volume is not a factor causing increased cardiac output in anæmia.

2. Specific Gravity of the Blood.—Among the mechanical factors which might conceivably influence the cardiac output in anæmia is the altered specific gravity of the blood. The specific gravity varies directly with the volume of the red corpuscles (Simon[18]) and with the hæmoglobin (Hammerschlag[2]). It is, therefore, diminished in anæmia. It might be supposed that the heart would have less work to do in forcing the lighter blood through the veins, so that the circulation would be facilitated. Certain simple considerations, however, show that the effect of changed specific gravity

would be negligible. The normal specific gravity of the blood is between 1055 and 1066, the specific gravity of plasma being 1028 to 1032, and that of corpuscles 1090. If there were no corpuscles present, the change in specific gravity would amount to only 2% to 3%, and even if the whole of the circulating fluid were water, the change would only be of the order of 6%. Not only is the change in specific gravity very small, but changes of this magnitude would have a negligible effect upon the work of the heart. This is evident from the formula[1] (Evans,[1] 1918) for calculating the work of the left ventricle:

$$W = \frac{7}{6} QR + \frac{wV^2}{2g}.$$

In this formula w stands for the weight of blood expelled at each contraction; but since the whole expression wV^2, representing the energy required to impart a certain velocity (V) to the mass of blood ejected during ventricular contraction, is almost negligible at rest, it follows *a fortiori* that slight changes in w would have practically no influence upon the work of the heart.

3. Diminished Viscosity.—Poiseuille[19] (1840, 1841, 1843, 1847), a medical graduate of Paris, was the first to recognize the important influence of viscosity upon the circulation, and on this account he must be regarded as among the founders of hæmodynamics. According to the law which he deduced from experiments upon the flow of defibrinated blood and other liquids along fine tubes, the rate of flow is inversely proportional to the viscosity and proportional to the fourth power of the diameter of the capillary. The law is expressed by the formula:[2]

$$Q = k \frac{HD^4t}{L}.$$

It is plain that since viscosity has such a marked influence upon the rate of flow through capillary tubes, it ought to have an important bearing upon the blood flow in anæmia, in which marked variations in viscosity occur. In blood the viscosity is due to the internal friction between the layers of plasma and the surface of the corpuscles (Hess,[11][12] 1910, 1920), and only to a much less extent to friction between the layers of the plasma itself. (See Figure XXIII.)

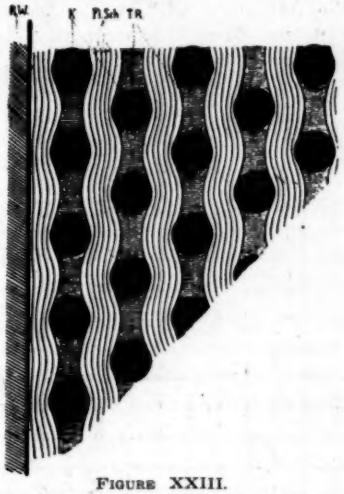

FIGURE XXIII.

Illustrating the theory of viscosity in heterogeneous systems, such as blood. *R*: fixed particle; *Fl.Sch.*: layers of fluid; *T.R.*: dead space; *R.W.*: wall of tube. [After Hess (*Kolloid Zeitschrift*, Volume XXVII, 1920).]

The corpuscles may be treated as fixed and the plasma as moving along the spaces between them with varying velocities, slowest near the wall and greatest near the centre of the vessel (see Figure XXIV). The flat shape of the corpuscles and the fact that when crowded together in narrow passages

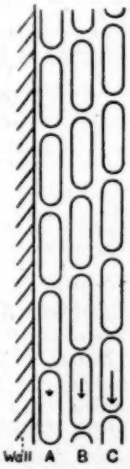

FIGURE XXIV.

Diagram of the flow of corpuscles along the wall of a capillary. The arrows represent by their direction and length the direction and velocity of each row of corpuscles. The corpuscles are shown moving edgeways. [After Trevan (*Biochemical Journal*, Volume XII, 1918).]

[1] W = work; Q = quantity (cubic centimetres) of blood expelled at each contraction; R = average arterial resistance or pressure during the outflow of blood from the heart expressed in terms (metres) of the height of a column of blood (arterial pressure metres Hg × 13·6, the specific gravity of mercury); w = weight of blood expelled at each contraction in grammes; V = mean velocity at which blood is expelled; g = acceleration of gravity (9·8).

Thus, if stroke volume were 60 c.cm. and arterial pressure 100 mm. Hg: QR = 60 × 0·100 m. × 13·6 = 81 gramme metres; V = 0·5 metre per second.

If the specific gravity of the blood were 1060, then w would be

$$\frac{1060 \times 60 \text{ (stroke volume)}}{1{,}000} = 63{\cdot}6 \text{ c.cm.}$$

Hence $\frac{wV^2}{2g} = \frac{63{\cdot}6 \times (0{\cdot}5)^2}{2 \times 9{\cdot}8} = 0{\cdot}81$ gramme metre.

If the specific gravity of the blood were only that of water, the value for $\frac{wV^2}{2g}$ would be 0·76. In the first place, therefore, 0·81 is negligible as compared with 81, and, secondly, the difference between 0·81 and 0·76 being only 0·05, would make a negligible difference to the final value of W.

[2] Q = the quantity of liquid flowing out in unit time; D = the diameter of the capillary; L = the length of the capillary; k = the absolute coefficient of viscosity for the liquid being tested, distilled water being taken as the standard; H = the pressure.

they move edge foremost, cause the viscosity to be less than if they were spherical, since they are less liable to come into contact and the spaces between them are larger (Trevan,[20] 1918; Hess,[10] 1920). The greater the number of corpuscles *per centum* volume, the narrower will be the passages along which the plasma flows. Consequently the viscosity varies with the corpuscular volume (Trevan,[20] 1918; Bircher,[2] 1920). (See Figure XXV.)

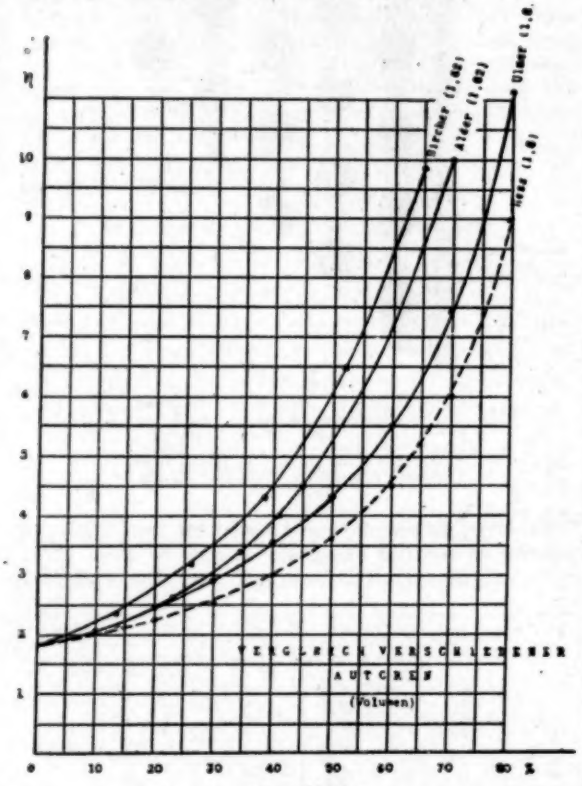

FIGURE XXV.

Curve showing relation of viscosity to corpuscular volume. Results of various investigators. [After Bircher (*Archiv für die gesammte Physiologie*, Volume CLXXXII, 1920).]

The viscosity coefficient of normal blood has been variously estimated (Hirsch and Bock,[16] 1901; Bence,[1] 1905; Determann,[4] 1906; Oswald,[18] 1907; Hess,[10] 1908; Welsh,[21] 1911; Hess,[11] 1920; Bircher,[3] 1921) at between 4·5 and 5·4, being slightly higher in males than in females. Much lower figures have been observed in anæmia. Of the total viscosity, it is computed that about 40% is due to the plasma and 60% to the corpuscles (Fahr and Ronzone,[8] 1922). The effect of a fall in the viscosity of the blood would be to make it easier for the blood to flow through the vessels, and therefore to diminish the peripheral resistance. This by itself would lead to a fall in blood pressure, but in anæmia the blood pressure is usually normal or only slightly diminished, except in cases with very low values for corpuscular volume and hæmoglobin (less than 50% of the normal). Lyon[17] records a definitely lowered blood pressure in anæmia, which he correlates with diminished viscosity; but this correlation is denied by Welsh.[17] Since the blood pressure is the product of two factors, the cardiac output and the peripheral resistance, it follows that in order to compensate for the fall in viscosity there would have to be an increase either in the peripheral resistance (vasoconstriction) or in the cardiac output, or both together. The effect of a fall in blood pressure is to bring into play the pressure reflexes through the carotid sinus and arch of the aorta. These consist in stimulation of the vasomotor centre (comprising the so-called arteriomotor and veno-motor centres), the adrenalosecretory centre, the cardioaccelerator and augmentor centre, and the respiratory centre; and in inhibition of the cardioinhibitory and vasodilator centres (Heymans, Bouckaert and Regniers,[15] 1933; Hering,[13] 1927). All these actions result in vasoconstriction, contraction of the spleen, cardiac acceleration, and probably increased cardiac output, although the last named has not been satisfactorily demonstrated in experiments upon the pressure reflexes of the carotid sinus.[14] The relative importance of vasoconstriction and increased cardiac output in maintaining the blood pressure is difficult to assess, and sufficient experimental evidence is lacking. Inspection of the curve of blood viscosity shows that the steepest part of the curve occurs as the corpuscular volume falls from 100% to 50%, after which it becomes flatter. Even with corpuscular volumes between the normal value (35% to 40%) and 50% of the normal (about 20%), the fall in viscosity is much steeper (amounting to just under 50%) than at lower levels. We have seen, however, that with hæmoglobin and corpuscular volume values between 100% and 50% of the normal, there is only a slight increase in cardiac output, while with hæmoglobin values below 50% the cardiac output rises sharply, while the viscosity changes little. This suggests either that slight changes in viscosity have a relatively greater effect when the viscosity is much diminished or that some other factors come into play to increase the cardiac output when the hæmoglobin falls below 50%. The nature and importance of those other factors now call for consideration.

Chemical Factors.—The presence of characteristic changes in the oxygen and carbon dioxide tensions in anæmia points to the possibility that chemical factors may be involved in the production of increased cardiac output. What has been said regarding the threshold level of tissue oxygen tension at which tissue respiration is liable, in the absence of compensatory changes, to become impaired, together with the fact that this level is reached when the hæmoglobin falls below 50%, suggests that changes in oxygen tension may be of primary importance. The first question to be settled, therefore, is whether there is any evidence that oxygen lack causes an increase in cardiac output.

1. Oxygen Lack and Cardiac Output.—The evidence regarding the effect of anoxic anoxæmia upon the cardiac output is conflicting.

Negative Results.—Doi,[13] using the Fick method, could find no increase in the cardiac output of cats under urethane anæsthesia when the oxygen in the inspired air was 13·31% and the arterial blood 81% saturated with oxygen. Greene and Greene[2] (1922), in experiments on the effects of progressively induced anoxic anoxæmia in dogs under chloretone or chloretone and ether, obtained no increase in minute volume. As regards observations on man, Hasselbalch and Lindhard[28] could not demonstrate an increase in minute volume as a result of lowering the percentage of oxygen in the air in the pneumatic cabinet. In the 1923 expedition to the Andes (Barcroft, Binger, Bock, Doggert, Forbes, Harrop, Meakins and Redfield[3]), the results for cardiac output depended on the method employed. With the carbon dioxide triple extrapolation method (Redfield, Bock and Meakins,[42] 1922), the values for cardiac output were the same at Cerro de Pasco (14,200 feet) as at sea-level; when the carbon dioxide method of Meakins and Davies[40] (1922) was used, the output was found to be slightly increased (one to two litres per minute) at Cerro.

Positive Results.—Barcroft[2] (1921) and Barcroft, Boycott, Dunn and Peters[1] (1919) produced oxygen lack in unanæsthetized goats by poisoning them with phosgene, which causes œdema of the lungs and interferes with the diffusion of oxygen from the alveoli into the blood. They found that the cardiac output (by Fick's method) was increased; but pulmonary reflexes and carbon dioxide retention prevent the result from being clear cut. Dreyer[15] (1926), measuring the cardiac output by means of the cardiometer, found an increased output in cats in experiments upon anoxic anoxæmia in which the arterial oxygen saturation was as low as 50% and 60%. Harrison[26] (1927) reported a marked increase in cardiac output in morphinized dogs and trained unanæsthetized dogs in the presence of severe anoxæmia (Fick's method). Harrison, Wilson, Neighbors and Pilcher[27] studied the threshold at which the increased output begins and found that it occurred when the arterial oxygen saturation was between 70% and 80% (man 75% to 80%, *vide sequente*). On the other hand, the oxygen consumption was not diminished until the arterial saturation fell to 50%, showing that there was a margin between the threshold of reaction and the threshold of failure. They also found that the stroke volume was markedly increased and the arterio-venous oxygen difference diminished. Gollwitzer Meier[18][20] (1928 and 1929), in similar experiments on dogs, has shown that with oxygen pressures between 120 and 100 millimetres of mercury in the inspired air, there was no significant change in minute volume, but between this and 40 millimetres of mercury pressure a rise in cardiac output occurred sooner or later (between 60 and 90 millimetres of mercury oxygen pressure, or 8% to 12% oxygen), while at pressures below 40 millimetres of mercury the output was diminished owing to cardiac failure. Sands and de Graff[46] (1925) also report that while oxygen lack may increase the cardiac output, "circulatory crises" occur at a certain level of anoxæmia, resulting in diminished output. Grollman[23] (1930), using his acetylene method[22] (1929), has reinvestigated the question of anoxæmia in cardiac output in man, both as regards the effects of high altitudes and breathing gas mixtures containing low percentages of oxygen at ordinary atmospheric pressure. He found that on ascending Pike's Peak (14,109 feet) there was a delay of about twenty-four hours in the rise in cardiac output; the output then rose gradually, reaching a maximum in about five days, the increase amounting to 45%; thereafter it declined, returning to its sea-level value at about the tenth day. The decline was correlated with the rise in the hæmoglobin content of the blood, and the return to the normal coincided with the attainment of the height of the compensatory polycythæmia. The cause of the delay in the rise of cardiac output is uncertain. It may be dependent upon such factors as changes in the peripheral circulation due to acapnia (the result of overbreathing due to anoxæmia) or sudden exposure to cold in unacclimatized persons, while changes in blood volume due to dehydration may also have played a part. In any case, the partial pressure of oxygen in the atmosphere at 14,109 feet would just barely correspond to the threshold at which significant changes occur in the cardiac output at rest (the same applies to the observations of Cerro de Pasco). When anoxæmia was induced by breathing mixtures of air and nitrogen, Grollman[23][25] (see Figure XXVI) observed that no change in cardiac output took place until the oxygen in the inspired air fell to about 11·6%, corresponding to an altitude

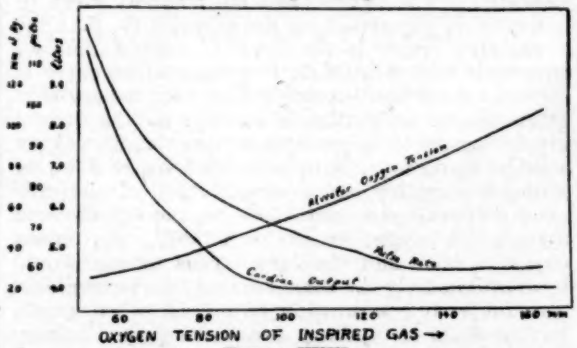

FIGURE XXVI.
Curves showing relation between oxygen tension in the inspired air and cardiac output and pulse rate. [After Grollman (*American Journal of Physiology*, Volume XLIII, 1930).]

of 15,000 feet; with lower oxygen pressures an increase amounting to 9% to 116% occurred. At this oxygen tension in the inspired air the arterial oxygen saturation was about 83%, which is evidently the threshold at which this form of oxygen lack causes increased output in man. Allowing for differences in the response of different species and different individuals, it is remarkable that the threshold in man should be very similar to that observed in the animal experiments above cited for dogs and cats. It may be noted that in Doi's experiments on cats, in which no increase in cardiac output was observed, the arterial saturation had not

fallen below this level. In order to bring these observations on anoxic anoxæmia into line with anæmia, it is necessary to find what venous and capillary oxygen tensions would correspond to this degree of arterial anoxæmia, and what degree of anæmia would cause the corresponding change in oxygen tension in the venous and capillary blood. With 100% hæmoglobin and 83% oxygen saturation, the oxygen content of the arterial blood would be 16 volumes *per centum*. If 5·5 volumes were removed in the passage through the capillaries, the venous oxygen content would be 10·5 volumes *per centum* or an oxygen saturation of 50%. At this oxygen saturation the oxygen tension of the mixed venous blood would be (by reference to the normal oxygen dissociation curve of hæmoglobin) 25 millimetres of mercury. In some of Grollman's experiments in which the arterio-venous difference was slightly less than 5·5 volumes *per centum*, the venous oxygen tension was slightly higher, 27 millimetres. Reference to Table I in Part I shows that to obtain a corresponding degree of venous unsaturation in anæmia the hæmoglobin would have to be reduced to 60%. Actually, however, the marked increase in cardiac output in anæmia does not as a rule begin until the hæmoglobin falls to 50% or below, which would give a venous oxygen tension as low as 23·5 millimetres of mercury. The difference between the figure for anæmia (23·5 millimetres) and that for anoxic anoxæmia (27 millimetres) is very small and becomes negligible when the difference between the oxygen dissociation curves of normal and anæmic blood is taken into consideration. The figure (23·5 millimetres) given in the table is calculated on the assumption that the dissociation curve is the same as normal; but we have seen that in anæmia the dissociation curve is shifted to the right, which means that hæmoglobin gives up its oxygen more readily, so that for a given degree of unsaturation the venous oxygen tension would not fall to as low a level as it would if the dissociation curve were normal. It is probable, therefore, that with 50% of hæmoglobin and an arterial oxygen saturation of 96%, the venous oxygen tension and capillary oxygen tension would be approximately the same as when the hæmoglobin was 100% and saturation 83%. In other words, the threshold of capillary and tissue oxygen tension at which the circulation responds by an increase in cardiac output, is the same for anæmia as for anoxic anoxæmia. The experiments of Campbell[10][11] already referred to (Part I) show that the oxygen tension in the peritoneal cavity may be much the same (27 millimetres of mercury), whether oxygen lack is produced by breathing 11% of oxygen (the threshold level for inspired air) or by reducing the hæmoglobin to 50%. These results for the direct estimation of tissue oxygen tension in a rabbit serve to confirm those obtained in the observation just cited.

Most of the discrepancies between the conclusions of different observers in regard to the effect of oxygen lack upon the cardiac output can be accounted for by such factors as the oxygen tension not falling below the critical level, the effect of anæsthetics, trauma due to operative procedures, excitement giving abnormally high values during the control period before the induction of anoxæmia, acapnia causing peripheral failure, and excessively low oxygen tensions giving rise to cardiac or respiratory failure.

The conclusion to be drawn from the data presented is that there is a close correlation between the development of oxygen lack (low capillary and tissue oxygen tension) and the increase in cardiac output. This is well brought out by comparing the curve for cardiac output (see Figures XX and XXI) with increasing degrees of anæmia with the curve showing the calculated fall in venous oxygen tension which would occur in the absence of any compensation (see Figure XXVII), and which may

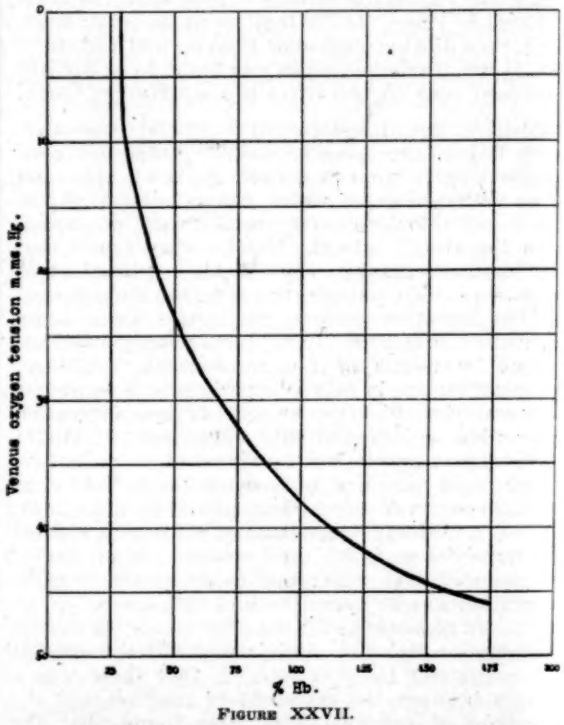

FIGURE XXVII.

Curve showing calculated venous oxygen tension with various percentages of hæmoglobin in the blood, assuming a constant arterio-venous oxygen difference of 5·5 volumes *per centum* and a constant oxygen consumption and cardiac output.

be regarded as indicating the stimulus to the circulation. It will be seen that both curves rise with increasing sharpness as the hæmoglobin falls below 50%. These curves may be contrasted with that for blood viscosity (see Figure XXV) which has its maximum steepness with hæmoglobin values or corpuscular volume greater than 50% of the normal.

We have yet, however, to account for the small rise in cardiac output which is observed in the presence of hæmoglobin values above the threshold at which the chemical stimulus to the circulatory mechanism comes into play.

This increase — about one litre per minute or 25% — probably represents that which is to be attributed to diminished viscosity. In polycythæmia, in which the viscosity is increased, the cardiac output is either unchanged (Mohr,[41] 1913; Röver,[45] 1911; Ernst,[17] 1930), in spite of increased blood volume (Bock,[7] 1921; Brown and Keith,[18] 1923; Brown and Giffin,[9] 1926; Keith, Rowntree and Geraghty,[33] 1915), or diminished (Bergmann and Plesch,[4] 1911; Loewy,[38] 1909; Liljestrand and Senström,[35] 1925; Blumgart, Gargill and Gilligan,[6] 1931), which also suggests that viscosity influences to some extent the cardiac output.

Although the effect of diminished viscosity may not be very great by itself, it may become more important when taken in conjunction with the chemical stimulus to the circulation. If a 25% increase occurs, other things being equal, then if the effect of the added chemical stimulus were to be augmented by 25%, the increase attributable to viscosity might be considerable and become of increasing magnitude as the cardiac output increased. The problem is complicated by the changes in the diameter of the vessels; nevertheless, the mechanical effects of viscosity would be of importance, especially as the local effect of chemical stimuli in the more active tissues, in which the circulation is greatest, would be to dilate the vessels. It would, therefore, appear that in anæmia the conditions are even more favourable to an increase in cardiac output than in anoxic anoxæmia. There is the same stimulus of oxygen lack, but in addition the viscosity is diminished (contrast this with the increase in viscosity associated with the polycythæmia of high altitudes and chronic oxygen lack), the carbon dioxide tension is normal at rest instead of being very low, so that acapnia and consequent contraction of capillaries are not present to militate against an increase in blood flow. It is perhaps because of the exceptional ease with which the circulation increases that there is less call for a compensatory increase in respiration at rest.

The analogy between anoxic anoxæmia and anæmia extends to the manner in which the increased cardiac output is achieved, in so far as in both conditions there is an increase in stroke volume.

2. Carbon Dioxide and Cardiac Output.—Such observations as are available show that the venous and tissue carbon dioxide tensions in anæmia at rest are almost within normal limits. This is a result of compensatory changes, as without these the difficulty which the blood has in taking up carbon dioxide would lead to a rise in carbon dioxide tension. The fact that the tissue carbon dioxide tension is so close to normal may have important results in a condition in which oxygen lack is present, for it is known that oxygen lack augments the response of structures such as the carotid body (and through it the respiratory centre) and the vasomotor centre to normal carbon dioxide tensions. Therefore it is necessary to inquire what influence carbon dioxide has upon the cardiac output. As in the case of anoxæmia, the experimental evidence is conflicting.

Negative Results.—Liljestrand,[35] 1919, using Krogh and Lindhard's[34] method for determining cardiac output, could find no evidence of an increase in minute volume when the alveolar carbon dioxide tension was raised by artificially increasing the dead space. Lindhard,[37] 1916, using the same method, could likewise find no increase in output on breathing 4% carbon dioxide. Douglas and Haldane,[14] 1932, obtained negative results on breathing 2% carbon dioxide. Grollman, 1930, using the acetylene method, finds that breathing carbon dioxide causes no increase until a concentration of over 6% is used and then the increase in output is such as might be attributable to the mechanical effects of increased respiration. Eppinger, Kisch and Schwarz,[16] 1927, likewise find that breathing high concentrations of carbon dioxide causes an increased output. Marshall,[39] 1936, reports that in the dog carbon dioxide inhalation actually causes a diminution in minute volume.

Positive Results.—The contrast between the effect of acapnia, which diminishes cardiac output, and the restorative effects of carbon dioxide in that condition led Henderson,[29][30] 1909-1918, to suppose that carbon dioxide increased the cardiac output. Itami,[32] 1913, and Riml,[44] 1937, report an increased output with comparatively low concentrations of carbon dioxide, and stress the point that with concentrations above 8% vasoconstriction occurs and cardiac output is diminished.

In considering these conflicting results, it is necessary to point out that the reaction of the body to the inhalation of a gas which is normally present in only very small concentration in the atmosphere, may be very different from those reactions which occur when the body is engaged in eliminating this gas. In some animals the inhalation of carbon dioxide leads to a slowing of the pulse rate (Traube,[47] 1865; Hill and Flack,[31] 1906; Cobet,[12] 1923), although this has not been found to be the case in man. This suggests the possibility that carbon dioxide when inhaled might irritate the upper respiratory passages (Traube,[47] 1865; Winterstein,[48] 1909) and reflexly inhibit the heart. Gollwitzer-Meier,[19] 1929, has brought forward evidence in support of this view. She confirms the fact that as a rule no increase in minute volume occurs during the inhalation of carbon dioxide in dogs. Immediately the inhalation is stopped, however, a sharp rise in cardiac output occurs and, like the polypnœa, continues until the carbon dioxide tension in the blood returns to the normal; but the increase in minute volume is out of proportion to that in respiration. That is interpreted to mean that after the removal of reflex inhibition the heart is able to respond to the increased venous inflow. If the vagi are cut, inhalation of carbon dioxide fails to cause any slowing of the heart.

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The Mechanism of Increased Cardiac Output.

Much of our knowledge regarding the mechanism by which the cardiac output is increased has come from the endeavour to explain what happens during muscular exercise. In muscular exercise the contraction of muscles acts as a pump which aids the venous return, while in addition to the voluntary impulses from the cortex to the muscles, impulses also pass from the cortex to the medullary centres (cortical overflow) controlling the activity of the heart and vessels. In anoxæmic conditions, including anæmia, and in the resting condition, no such factors are operative. We are dealing here with the response of the circulation to a chemical stimulus. There are three possible ways in which the cardiac output may be increased at rest:[81][82] (i) increase in cardiac activity, (ii) increase in blood volume, (iii) diminution in the capacity of the blood reservoirs.

As regards the first of these, experiment shows that sectioning the vagi (Bock and Bauchholtz,[19] 1920, Harrison Blalock *et alii*,[54] 1925) or paralysing the vagus endings with atropine (Harrison,[54] Blalock *et alii*, 1925) produces only an insignificant (at most 4%) increase in the minute volume, in spite of doubling the heart rate. Similarly, stimulation of the accelerans is found to cause only a slight (at most 15%) increase in the output as measured either by the blood flow (Pawlow,[100] 1881) or by means of the cardiometer (Lehndorff,[90] 1909). Excessive acceleration, so far from increasing the cardiac output, may actually diminish it owing to encroachment upon the rapid part of the period of diastolic filling (Henderson,[58][59] 1906, 1909, Barcroft,[8] 1921, Wiggers,[112] 1923). The fact that the heart, in spite of its being the propelling agent in the circulation, is unable to increase its output to any great extent primarily through its own activity, is due to certain fundamental facts about its mode of functioning. The heart is a pump, but it is a pump of a peculiar kind: it does not suck in the fluid, it has to pump out. The heart, even when it is freed from all its nervous connexions and is therefore unable to accelerate, as in the heart-lung preparation, responds to increased inflow by increased output, the increased pressure on the afferent side leading to increased diastolic filling, which is followed by increased systolic discharge (Knowlton and Starling,[86] 1912, Patterson, Piper and Starling,[99] 1914, Starling,[109] 1915, Straub,[112] 1914, Henderson and Prince[60] 1914). When the innervation of the heart is left intact, the organ also responds by acceleration and increased completeness of systole, owing to a nervous reflex (Bainbridge reflex), the effective stimulus being the rise of pressure in the region of the great veins at their entrance to the heart (Bainbridge,[6] 1915, Anrep[3] and Segall, 1926).

This reflex, the afferent path of which is through the vagus, results in a diminution of vagus tone and an increase in accelerator tone. The output of the heart, therefore, is dependent upon the venous return, and the heart delivers to the periphery only what is brought to it. The activity of the left ventricle is only a limiting factor, in so far as the filling of the veins and the venous pressure are dependent upon the residuum of energy derived from ventricular contraction after the blood has passed through the peripheral vessels. Since the activity of the heart plays only a minor rôle in causing increased cardiac output (Jarisch,[82] 1929, Gollwitzer-Meier,[46] 1929), we must look to the other two factors to explain the increased venous return and increased pressure in the great veins. An increase in blood volume will do this, and is accompanied by increased cardiac output. This can be demonstrated in the closed circuit heart-lung preparation (de Burgh Daly,[27] 1925), as well as in the intact animal. As already pointed out, increased blood volume is not the cause of increased cardiac output in anoxæmia, nor in most forms of anæmia. We are therefore left with the third possibility, namely, that the increased output is due to a diminution in the capacity of the blood reservoirs. Such a diminution has much the same effect upon the venous return and pressure in the great veins as injecting a greater volume of blood into the active circulation. It is the reciprocal

of increasing the blood volume. The problem therefore resolves itself into a consideration of how the capacity of the vascular reservoirs can be diminished and whether the diminution can be brought about by oxygen lack and carbon dioxide or by the reflexes which compensate for the diminished viscosity of the blood in anæmia.

As the capacity of the arterial system is very small as compared with that of the venous system and capillaries, arteriolar constriction will have very little effect upon the amount of blood in active circulation. Moreover, only those parts of the vasculature can act as blood reservoirs which can diminish their capacity without producing any significant increase in the resistance to the flow of blood. Changes in the arterioles are more concerned with alterations in the distribution of blood in the body, the tone of the arterioles having to do chiefly with the regulation of the blood pressure, and especially with keeping the blood pressure at a sufficient height to maintain an adequate blood flow through the coronary and cerebral vessels. The spleen[9][53] and the subpapillary venous plexus of the skin[10][116][114][115][97] are blood depots of the first order, in that blood can stagnate in sinuses or diverticula from the main blood stream and by emptying themselves they can add to the volume of actively circulating blood. An interesting problem arises here as to what would be the effect of splenectomy or diseases of the spleen upon the ability to increase the cardiac output. Krogh[87] (1912) also suggested that the portal system, intercalated as it is between two resistances, each under the control of the nervous system, could play the part of a blood reservoir, and that by contraction of the portal vein and its branches blood could be expelled into the central veins and so towards the heart. Bauer, Dale, Poulsson and Richards[12][26] have shown that splanchnic stimulation causes not only contraction of the portal vessels, but also relaxation of Mautner and Pick's[96] sphincter at the exit of the hepatic veins. As the blood in the liver and mesenteric veins is not contained in diverticula, they constitute a blood reservoir of a second order (Barcroft[11]).

Barcroft computes that the blood stored is distributed roughly as follows: liver, 20%; spleen, 16%; and skin, 10%; but the capacity of these reservoirs is susceptible of wide variation. Donegan[28] and Hooker[74][75][76] demonstrated that the veins as well as the arteries are under sympathetic control, and Donegan[28] and Fleisch[37] have found that different veins show different degrees of response. Those of the mesentery are the most sensitive, those of the skin come next, while the veins from muscles and the large central veins show little, if any, response. The mechanism therefore seems to be designed to allow of free exit of blood from muscle capillaries and to drive the blood towards the central veins.[51][102] The veins also exhibit rhythmic contractions (Gollwitzer-Meier,[43][44][45]) resembling the Traube-Hering waves, evidently due to overflow from the respiratory centre to the venomotor centre, which is part of the vasomotor centre. It has been found that both oxygen lack and carbon dioxide[47] cause contraction of veins, and Gollwitzer-Meier[42][43][48] has shown that section of the splanchnic nerves not only abolishes the contraction of the mesenteric veins, but abolishes or diminishes the rise of pressure in the *vena cava* and the increase in cardiac output. This effect is therefore evidently dependent upon the action of oxygen lack and carbon dioxide upon the autonomic nervous system.

In regard to the spleen, de Boer and Carroll[13] have demonstrated that oxygen lack, induced either by carbon monoxide or by breathing atmospheres deficient in oxygen, causes contraction of that organ, this action being dependent upon stimulation through the splanchnic nerve by impulses originating either in the vasomotor centre or in the spinal cord. The latter observation is of interest, as Harrison, Blalock, Pilcher and Wilson[54] (1927) found that oxygen lack caused an increase in cardiac output, even after denervation of the heart or cutting off the blood supply to the medullary centres. The effect of carbon dioxide alone upon the spleen does not seem to have been recorded, although asphyxia has been found to cause contraction.[105][14][15][16][38][49]

Both oxygen lack and carbon dioxide stimulate the vasomotor centre, and although they act synergically,[102] their mode of action is slightly different. Both stimulate it indirectly through their action upon the chemo-receptors of the carotid body.[65][66][68][69] In addition, carbon dioxide directly stimulates the centre itself;[67] but it is believed that oxygen lack of the centre, while increasing its activity, acts indirectly by sensitizing the centre to the action of carbon dioxide.[70][67]

A difficulty arises in the case of anæmia in respect of the effect of the blood changes upon the carotid body. All our knowledge of the effect of blood gases upon the chemoreceptors has been obtained with blood in which the tension of these gases in the arterial blood was altered. In order that anæmia might have any effect upon the chemoreceptors it would be necessary for the metabolism of the carotid body to be sufficiently high to reduce the oxygen tension in the blood traversing it below the threshold necessary to cause stimulation, or to produce more carbon dioxide than could be adequately removed by the blood. Of this we have as yet no evidence. The stimulation of the vasomotor centre produces arteriolar constriction,[60][83][95][35] but this is offset by the dilatation of capillaries[92][70] caused by the local action of both oxygen lack and carbon dioxide in the active tissues and by the compensatory action of the pressure reflex through the carotid sinus. The result is that acute anoxic anoxæmia produces only a slight rise in blood pressure in man,[107][108] carbon dioxide little, if any, and anæmia none at all, possibly owing to the added factor of diminished viscosity.

The importance of carbon dioxide as a cause of capillary dilatation in anæmia is difficult to assess,

as it is unknown whether the carbon dioxide tension at rest rises above the threshold necessary to bring about relaxation; but perhaps even a normal tension may have a greater effect in the presence of low oxygen tension. The dilatation of capillaries in the active tissues and the vaso-constriction elsewhere cause a shift of blood from such parts as the skin and portal system to the muscles. This may account for the observation of Schneider and Truesdell[107][108] (1923), that marked or long-continued anoxæmia causes a diminished blood flow through the hand. Similarly, in anæmia, Stewart[110] (1912), using his calorimetric method, demonstrated that the blood flow through the hand was diminished, while Fahr and Ronzone[36] (1922), who examined the skin capillaries under the microscope, report a reduction in their number in anæmia.

A number of other adjustments enable the heart to respond to the increased demands upon it. Both oxygen lack (Hilton and Eichholtz,[72] 1922, Hochrein,[73] 1932) and carbon dioxide [4][5][7][94] dilate the coronary vessels—both the capillaries and the terminal portions of the arterioles[5]—but the effect of oxygen lack is much the greater of the two, being proportional to the tension of oxygen.[72]

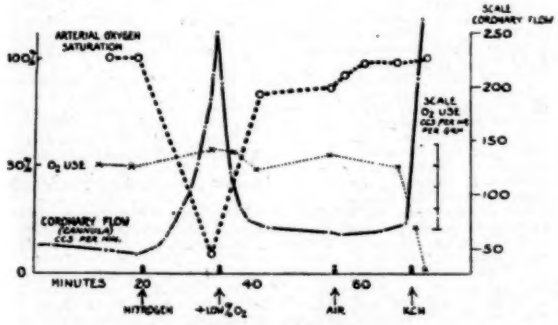

FIGURE XXVIII.

Curves showing relation of the coronary blood flow and of oxygen consumption by the heart to the degree of oxygen saturation of the blood passing through the coronary vessels. [After Hilton and Eichholtz (*Journal of Physiology*, Volume LIX, 1925).]

(See Figure XXVIII.) As in the case of the carotid body, it is unknown what effect anæmia, as distinct from arterial anoxæmia, has upon the coronary vessels. It is probable, however, that, as in other muscular organs, an abnormal desaturation of the blood takes place and that the resulting low oxygen tension dilates the vessels. The coronary vessels are also dilated through a reflex from the heart (Anrep,[4][5] 1926), when it is in a state of increased activity, as it is in anæmia. This reflex is apparently distinct from the Bainbridge reflex, although, like the latter, it gives rise to diminished vagus tone and increased sympathetic tone, and the vagus is constrictor while the sympathetic is dilator to the coronary vessels.

Both oxygen lack and carbon dioxide affect the cardio-regulator centres in the medulla. Slight degrees of oxygen lack do not produce much effect at rest, but with increasing degrees of oxygen lack there occur both an increase in accelerator tone[85][91][24] and a diminution in vagus tone,[42][3] with resulting quickening of the heart rate. The effect of carbon dioxide has not been so clearly demonstrated. Inhalation of carbon dioxide, as we have seen, reflexly stimulates the vagus centre and may thus slow the heart, or at all events prevent acceleration. It is claimed, however, that if the carbon dioxide tension in the neighbourhood of the medullary centres is increased, there occurs, as in the case of oxygen lack, an increase in accelerator tone and a diminution in vagus tone (Gollwitzer-Meier,[47][46] 1929) and consequently increased heart rate, but these results require confirmation by other methods.

Very little is known regarding the effect of either oxygen lack or carbon dioxide upon the carotid body or sinus in so far as reflex action upon the cardio-regulator centres is concerned. Heymans, Bouckaert and Samaan[71] state that only concentrations of carbon dioxide above physiological limits cause acceleration, which they suggest may be due to paralysis of the tensor receptors.

Among the effects of oxygen lack upon the brain is the stimulation of the adrenalo-secretory centre. The centre, as we have seen, is also stimulated through the carotid sinus and aortic arch reflex mechanism by the fall in blood pressure which would result from diminished viscosity. That asphyxia could cause increased secretion of adrenaline has been demonstrated by Cannon[20] and others,[31][2] although this has been denied.[41][111] Kellaway,[84] however, has studied the effects of oxygen lack and carbon dioxide separately, and has shown that while oxygen lack, even of mild degree, stimulates the secretion of adrenaline, carbon dioxide has very little action of this kind.

The effects of adrenaline upon the circulation are very similar to those of oxygen lack and carbon dioxide, but it is not to be supposed that the action of the blood gases is dependent upon adrenaline secretion, as their effects are observed even after ablation of the adrenal glands.[91][92][43][13] Like oxygen lack and carbon dioxide, adrenaline causes an increase in cardiac output,[32][33][82][101] contraction of the spleen,[93][105][78][55] dilatation of capillaries,[21][25][26][39][77] constriction of arterioles[98] (except the coronary vessels, which are dilated[29][30][19][5][94][56][88]), constriction of veins,[1][52][28][57] especially those of the portal area[17][19][22][23][26][93] and subpapillary[76][57] plexus of the skin, and it causes relaxation of Mautner and Pick's sphincter.[12][26][96] The action of adrenaline upon the vessels and spleen is, however, entirely peripheral, depending upon stimulation of the sympathetic nerve endings or upon a direct action on the capillary walls, especially those of the coronary circulation; in addition, adrenaline directly stimulates the cardiac muscle.[2][7][34] Adrenaline has little, if any, direct action on the medullary centres,[62] and such effects

as different workers claim to have observed are of the opposite character to those produced by oxygen lack and carbon dioxide—depression of the vasomotor centre[106] and tonic action on the cardioinhibitory mechanism.[79][104] It accelerates the heart by stimulating the sympathetic nerve endings.[89][30]

From what has already been said regarding the effect of a fall in viscosity upon the reflex mechanism of the carotid sinus and aortic nerves, it will be seen that these reflexes result in changes in the heart and vessels very similar as regards their end results to those which have just been described in connexion with oxygen lack, carbon dioxide and adrenaline. It would, therefore, appear that all these mechanisms—oxygen lack, carbon dioxide, adrenal secretion, and pressure reflexes—act synergically in anæmia. Unlike anoxæmia produced by breathing atmospheres deficient in oxygen, there is no accompanying acapnia, and even although the carbon dioxide tension does not rise above the normal at rest, which is uncertain as regards man, it is possible that the threshold for the action of carbon dioxide may be lowered in the presence of oxygen lack. In anæmia there is also no increase in blood viscosity such as accompanies the polycythæmia of chronic oxygen lack, but a fall. Finally, as regards carbon dioxide, there is an absence of any of the reflex inhibition which occurs when the gas is inhaled. The conditions present in anæmia, therefore, seem to be more favourable to increased cardiac output than those associated with any of the various factors above mentioned taken singly.

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Respiratory Adjustments.

Owing to the exceptional efficiency of the circulatory adjustments in anæmia, there is correspondingly less need for respiratory compensation. This may partly help to explain why little, if any, change in the rate or depth of respiration may be detected by simple inspection of the patient, except in anæmia of marked degree. It cannot be inferred from this, however, that there is no increase in respiratory volume, as a change in the breathing not perceptible to the eye may be measured by suitable means. Without there being some increase in respiratory volume, it would be very difficult to explain the low alveolar carbon dioxide tension which has been reported[1][6] (see Part II). As the various factors which make for increased cardiac output also tend to increase the respiration,[11][12] some increase in respiratory volume might be anticipated, but the increase is probably less than that which would result from the same degree of oxygen lack or carbon dioxide excess produced respectively by breathing atmospheres deficient in oxygen or containing excess of carbon dioxide, even if the effects were added together. This, as already explained, is because either of these conditions by itself may be complicated by factors—acapnia and increased viscosity in anoxæmia, vagus inhibition in the case of breathing carbon dioxide—which militate against an increase in cardiac output. Besides, in anæmia there is the mechanical factor of diminished viscosity to aid the circulation. For these reasons the circulatory adjustments in anæmia more or less outdistance the respiratory adjustments.

The relative effects of the pressure reflex, oxygen lack and carbon dioxide excess upon the respiration in anæmia are difficult to assess in the absence of adequate experimental evidence.

The finding of a normal or slightly subnormal tissue carbon dioxide tension in experimental anæmia (Campbell[5]) suggests that some factor other than carbon dioxide retention may be responsible for the increased respiratory volume which we must assume is present when the alveolar carbon dioxide tension is lowest in anæmia. For reasons already given, however (Part II), it is not justifiable to argue from experimental anæmia in rabbits to the clinical anæmias in man. Stimulation of the respiration through the pressure reflex or by oxygen lack is the other factor to be considered. The pressure reflex may perhaps play some part in the lesser degrees of anæmias when the blood viscosity is falling most rapidly.

Oxygen lack is a common cause of over-breathing in arterial anoxæmia,[9][110] the lowered oxygen tension of the blood reaching the carotid body stimulating the chemoreceptors.[2][3][4][12][15][17] Oxygen lack does not stimulate the respiratory centre itself;[7][8][15][16][18][12][13] its direct effect on the centre is depressant. As already pointed out, however, uncertainty exists as to whether anæmic blood can stimulate the chemoreceptors, as it is unknown whether the metabolism of the carotid body is sufficiently active to desaturate the blood passing through it sufficiently to reduce the oxygen tension below the threshold at which the chemoreceptors are excited. This could be determined only by experiment. If the carotid body is not stimulated in anæmia, the individual should be able to tolerate greater degrees of oxygen lack in the tissues without hyperpnœa than in the presence of arterial anoxæmia. As the number of respirations per minute is usually about normal, except in profound anæmia, increased respiratory volume would have to be accounted for by an increase in the depth of respiration. This would not lend support to the view that oxygen lack stimulates the respiration, as an increase in rate rather than depth is characteristic of anoxic anoxæmia.[9][10] On the other hand, carbon dioxide increases the depth rather than the rate,[9] so that we return to the possibility that in clinical anæmias carbon dioxide retention may be responsible for the increased breathing. If, owing to the change in the carbon dioxide dissociation curve of blood, the carbon dioxide tension in the tissues was raised, even slightly, and at the same time only the normal amount of carbon dioxide was delivered into the blood and ultimately to the lungs per minute, then the stimulation of the respiratory centre by the retained carbon dioxide would cause over-breathing and would lower the carbon dioxide tension in the alveolar air. We would, therefore, be dealing with a unique state of affairs in which a low alveolar carbon dioxide tension coexisted with a raised carbon dioxide tension in the region of the respiratory centre.

Before we can accept this as an explanation of what occurs in anæmia, it will be necessary to have experimental data regarding the tissue carbon dioxide tension in clinical anæmias, and there the matter must rest for the present. The compensatory increase in cardiac output would tend to keep the tissue carbon dioxide tensions close to the normal level with a minimum increase in respiration; but when the circulation fails to compensate and the transport of carbon dioxide to the lungs becomes inadequate, the rise of carbon dioxide tension in the respiratory centre, and possibly in the carotid body,[2][3][13][14][15][17] would cause a marked increase in respiration.

The hyperpnœa which occurs during voluntary exercise in anæmia is probably due to the increased metabolism of the respiratory centre, and to the inadequate removal of carbon dioxide from the centre, which is subjected to stimulation by impulses from the cortex and through reflex channels.

In assessing the importance of various factors which may cause hyperpnœa in patients suffering from anæmia, it is necessary to bear in mind that

various things besides the anæmia as such may be responsible for increased respiration. For example, pyrexia, increased metabolism, pulmonary disease, accumulations of fluid or the development of swellings in the chest, abdominal tumours, enlargement of the liver and spleen, ascites when present in diseases which cause anæmia, may all embarrass the respiration and give rise to hyperpnœa or even to dyspnœa.

Increased respiration in anæmia is of very little advantage to the organism as regards the absorption of oxygen, as the oxygen saturation of the arterial blood is normal or perhaps slightly above normal owing to the low tension of carbon dioxide and consequently the higher tension of oxygen in the alveolar air. The respiratory compensation aids the elimination of carbon dioxide and serves to keep the carbon dioxide tension of the tissues as nearly as possible within normal limits, when circulatory adjustments fail to do so. The hyperpnœa may also aid the circulation by mechanically facilitating the venous return.

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Tolerance.

While the various compensatory mechanisms which have been described enable the functions of the organism to be carried on more or less efficiently, they may fail to restore the oxygen and carbon dioxide tensions in the tissues to the normal level. Provided, however, that the change in gaseous tensions is not produced too rapidly, the tissues become able to withstand the fall in oxygen tension.[4][7][8] The cells adapt themselves to the lower cellular oxygen tensions;[1][2] that is to say, they acquire tolerance towards the changed condition of their environment. This tolerance is most strikingly illustrated in those tissues the oxygen consumption of which is small, but which are normally very sensitive to changes in oxygen tension, and especially in the nervous system. The brain, for example, has a very low oxygen consumption, only about one-third that of resting muscle (Hill and Nabarro[6]), and a slight diminution in oxygen tension in the cerebral capillaries, if suddenly produced, causes faintness, nausea, giddiness and other disturbances of consciousness, or even unconsciousness. Sudden deprivation of oxygen will also cause hyperpnœa, partly owing to the sensitiveness of the carotid body to changes in oxygen tension and partly owing to the fact that it takes a time for carbon dioxide, which acts synergically with oxygen lack, to be eliminated. But if oxygen lack is slowly induced, much lower oxygen tensions can be tolerated without these disturbances.

In anæmias with insidious onset the conditions are such that tolerance would have plenty of time to develop and to reach a high degree.

With regard to the respiration, the development of tolerance cannot be entirely ascribed to a washing out of carbon dioxide, as has been suggested by Haldane[3][4][5] in the case of adaptation to low oxygen pressures. Campbell[2] has shown that different animals exhibit marked differences in tolerance, in spite of the carbon dioxide tensions found in their tissues being very similar. In anæmia a remarkable degree of tolerance is achieved, in spite of the tissue carbon dioxide tension remaining approximately normal (or perhaps being increased). Although the cells of the central nervous system may acquire tolerance to low oxygen pressures, they do not remain quite normal in the presence of the altered conditions of their environment. Mental disturbances and disturbances of consciousness, such as those above referred to, may remain in abeyance; but instead of these, fatigue and lassitude predominate.

Although little is known regarding the oxygen tension in the cardiac muscle, the fact that the heart becomes able to carry on its functions in the presence of very low oxygen tensions in animals exposed to atmospheres deficient in oxygen, is noteworthy, as lesser degrees of oxygen lack, if suddenly induced, may cause death from cardiac or respiratory failure. As to whether tolerance develops in voluntary muscle is also unknown. It is possible

that the demand of the resting muscle for oxygen may become less, and this may have something to do with the absence of an excessive rise of lactic acid in the blood in the presence of marked anæmia. Should further experiment show that the respiratory centre is depressed by oxygen lack but not stimulated reflexly by it through the carotid body, a further explanation of the apparently greater tolerance of low oxygen tensions in anæmia as compared with arterial anoxæmia may be found. This point is at present under investigation. There are few clinical phenomena more curious than the comparative comfort and freedom from symptoms of the patient with profound anæmia when he is at rest, who, but for the exceptional efficiency of the compensatory mechanisms and the development of a very high degree of tolerance, might be in a condition, so far as oxygen supply to the tissues is concerned, equivalent to that of living at the top of Mount Everest.

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FAILURE.

If anæmia is sufficiently profound or prolonged, the compensatory changes become inadequate, the limits of tolerance become exceeded, and failure sets in. If the hæmoglobin falls as low as 20%, the patient cannot hold out for long, and with hæmoglobin values below 30% there is the danger that severe and perhaps irreparable damage may be done if the condition is allowed to persist for any considerable length of time. It is remarkable, nevertheless, how complete recovery may be after fairly long exposure to severe oxygen lack due to anæmia or to high altitudes.[15] From what has been said about the manner in which the oxygen reserve of the blood is encroached upon in anæmia and about the call upon the circulation to compensate for deficient oxygen carrying power by increased cardiac output, the need for rest in anæmia is obvious. The conclusions to be drawn from this discussion of the various factors involved are in accord with the results of clinical experience. Patients with hæmoglobin percentages below 60, even although they do not exhibit symptoms, are best treated in bed; or, if they are allowed to get up, they should indulge in only a minimum of effort. With hæmoglobin values between 60% and 70% not more than gentle exercise on the level should be permitted.

Some conception of the strain upon the heart may be gained from a comparison between the work of the heart and the coronary blood flow during muscular exercise and in anæmia. A normal man doing the heaviest sort of muscular work would have a cardiac output of about 20 litres per minute or more,[5][6][14] and the coronary blood flow, as computed by Hill, would be as great as 1·4 litres per minute.[8] In patients with a hæmoglobin value of 20% (Haldane scale), Dautrebande found the cardiac output to be somewhat less than this, namely, 14·5 litres per minute. This figure itself implies that the work of the heart was greatly increased, and would correspond to that of a man doing work of moderate severity, but the effect of such an increase upon the coronary circulation is even more striking, as a rough calculation will show.

Suppose the output to be 14 litres per minute, and the hæmoglobin 20% on the Haldane scale, corresponding to an oxygen capacity of a little less than five cubic centimetres. As the diminution in blood pressure which is present in marked anæmia would diminish the work of the heart, we shall suppose that the mean blood pressure is 80 millimetres of mercury instead of the normal 100 millimetres. Then $\frac{14 \times 80}{760}$ = 1·60 litre atmospheres or 1,600 c.cm. atmospheres = 1,600 × 10^6 ergs[1] = 160 Joules[2] = 38 gramme calories.[3] If the mechanical efficiency of the heart were 20%, the figure would have to be multiplied by 5, giving 190 calories for the work of the left ventricle. As the work of the right ventricle is estimated at roughly one-quarter of that of the left, another 47 calories would have to be added to give the total work of the heart, namely, 237 gramme calories per minute. Now, at the average respiratory quotient 5 gramme calories are yielded by the combustion of one cubic centimetre of oxygen; therefore, 237 gramme calories would require 47 cubic centimetres of oxygen, and this is the amount of oxygen which the blood would have to supply to the heart muscle per minute. To find the minimum amount of blood necessary for this purpose we shall assume that the blood is completely reduced in traversing the coronary capillaries. If the oxygen capacity was five cubic centimetres, then, as this is the amount of oxygen in 100 cubic centimetres of blood, 47 cubic centimetres of oxygen will be carried by 940 cubic centimetres or nearly a litre of blood. If the oxygen content was only three cubic centimetres, corresponding to about 14% of hæmoglobin, a similar calculation would show that the coronary flow would have to be at least 1·56 litres, or rather more than that estimated by Hill for maximal effort in the normal individual. As the blood may not be

[1] One dyne per square centimetre = 0·9869 × 10^{-6} atmospheres, or one c.cm. atmosphere corresponds to 1,013,300 (roughly 10^6) ergs or dynes per square centimetre.
[2] One Joule = 10,000,000 ergs.
[3] One Joule = 0·2387 gramme calories.

fully desaturated in the coronary vessels and as the oxygen content of arterial blood is somewhat less than the oxygen capacity, the blood flow is probably greater than here estimated.

In view of these results it is little wonder that patients do not long survive with hæmoglobin values of 20% or below. Under such conditions the coronary circulation would tend to reach the limit of its capacity, and if further demands upon it could not be met, there would be failure of oxygen supply to the heart and consequent failure of the heart itself. Such an increase in the work of the heart would have an appreciable effect upon the basal metabolism. The normal heart consumes about 0·068 large calorie per minute, or 96 calories per twenty-four hours, which is about 4% of the basal metabolism. If the heart of the anæmic patient in the example given consumes 0·237 large calorie per minute or 341 calories in the twenty-four hours, then, subtracting the normal consumption of calories (96), the increase would be 245 calories or about 16% of the basal metabolism (1,500 calories). This probably accounts for most of the increase in basal metabolism attributable to compensation, although some allowance would have to be made for increased work of the muscles of respiration. As the heart in advanced anæmia has difficulty, even at rest, in increasing its blood supply sufficiently to supply itself with enough oxygen, it is obvious that if the work of the heart were increased as a voluntary exercise, the same difficulty would occur with lesser degrees of anæmia. In these circumstances not only would the heart itself suffer from oxygen lack, but it would fail to respond to the extra demands made upon it. That is to say, heart failure would occur. Exercise, therefore, is liable to have a deleterious effect upon the heart in anæmia.

A heart which has been weakened by oxygen lack may dilate, and cardiac dilatation was observed, for example, among those members of the Mount Everest expedition who went above 27,000 feet.[15] Cardiac enlargement has also been produced experimentally (Liere[13]). Marked dilatation of the heart is not, however, a feature of anæmia. Hypertrophy has been reported,[1][3] but it is remarkable that it is not observed oftener in view of the work which the heart may be called upon to perform. Perhaps oxygen lack and the degenerative changes in the cardiac muscle militate against the development of hypertrophy, while the time factor has also to be considered. (See Part IV.)

Since the heart in anæmia, as in anoxic anoxæmia, increases its output largely by increase in stroke volume, there may be little increase in the pulse rate at rest until the hæmoglobin falls to about 50%. A marked and continuous increase in pulse rate in anæmia when it cannot be accounted for by some complication, such as fever, is a sign of heart failure. It is analogous to what is observed in anoxic anoxæmia, and is referred to by Barcroft[2] as a "signal of distress". Gollwitzer-Meier[9] (1928), for example, in experiments upon the effects of progressive anoxæmia with the dog, showed that with oxygen pressures between 120 and 100 millimetres of mercury there was little, if any, change in pulse rate or in stroke volume; between 100 millimetres and 40 millimetres of mercury there was a moderate increase in both heart rate and stroke volume; when the pressure fell somewhat below 40 millimetres of mercury there occurred a marked increase in heart rate, but this was accompanied by diminished stroke volume and diminished cardiac output. With still further lowering of the oxygen tension the heart was slowed. This phase of terminal bradycardia is sometimes observed in anæmia, and is due to depression of the function of the sino-auricular node, owing to the vagus inhibition[10][11] which develops at a certain stage of oxygen lack—the reverse of what happens with lesser degrees of anoxæmia. The changes which occur in the cardiac rhythm during the various phases of anoxæmia have been studied electrocardiographically by Greene and Gilbert[10][11] (1921-1922). During the stage of acceleration the processes of conduction and contraction are both accelerated. In the stage of slowing there is a progressive suppression of sino-auricular rhythm, due to vagus inhibition and a development of various forms of heart block.

In anæmia, cardiac irregularities are not common, but the electrocardiographic changes during the stage of failure do not appear to have been studied in detail. Sudden death occasionally occurs in anæmia, but its cause is unknown. Among the evidences of cardiac failure and oxygen lack in anæmia is the development of œdema, but œdema may be due to other causes as well.

The fall in blood pressure may also be regarded as manifestation of failure. The weakened heart is unable to increase its output sufficiently to compensate for capillary dilatation; that is to say, a form of peripheral as well as cardiac failure may eventually set in.

Dyspnœa likewise is attributable to a failure of circulatory adjustment. When blood flow is not sufficiently increased to effect the adequate removal of carbon dioxide, there will be carbon dioxide retention and this will stimulate the respiratory centre even at rest. Oxygen lack and carbon dioxide excess in the carotid body may also be factors (*vide ante*) in stimulating the respiration, but this is doubtful.

In other forms of oxygen lack, Cheyne-Stokes respiration is common, but this does not occur in anæmia, probably because the carbon dioxide tension does not fall sufficiently to permit of apnœa. The retention of carbon dioxide may also account for the fact that in anæmia the heart does not continue to beat after the respirations have ceased, as it does in carbon monoxide poisoning and anoxic anoxæmia. In anæmia the respiratory centre is kept active by carbon dioxide, and it fails as a result of oxygen lack only when the circulation stops. When the heart is examined after death in animals which have succumbed to prolonged exposure to

low oxygen tension (Campbell,[4] 1927), it is found to be dilated, while congestion of the other organs is observed, suggesting that death was due to cardiac failure; but the congestion is probably only a terminal phenomenon. The heart itself shows fatty change very similar to that met with in anæmia. This similarity suggests that the fatty degeneration which occurs in anæmia is also due to the effects of oxygen lack. This may not, however, be the only factor responsible for fatty changes in the organs of patients suffering from diseases which cause anæmia. Among the other possible causes are: destruction of red corpuscles, liberating large quantities of lipoid material of which the envelope of the corpuscle is composed; depletion of plasma proteins, with resulting rise in blood cholesterol and deposition of cholesterol in organs, as in nephritis or after experimental removal of plasma proteins (cataphoresis); starvation due to anorexia or other cause, which brings about the mobilization of depot fat, the disappearance of glycogen from the liver and the deposition of fat (infiltration) in the cells of the viscera; finally, damage to cells due to toxæmia arising from the disease causing the anæmia.

The red corpuscles play some part in the transport of intermediate products of fat metabolism—phospholipines *et cetera* (Leathes and Raper[12])—but it is unknown whether the loss of corpuscles in anæmia results in any disturbance of this phase of fat metabolism.

In animals subjected to prolonged oxygen lack, emaciation is commonly observed,[3] and loss of weight also occurs at high altitudes.[15] This may be partly due to anorexia and partly to the effects of oxygen lack upon the glycogenic function of the liver. Perhaps some of the emaciation seen in anæmia may be due to these causes, but emaciation is by no means regularly met with in anæmic persons.

The absence of any rise in blood lactic acid much above the normal, even in profound anæmia, has already been remarked upon. The most likely explanation seems to be that owing to the increased activity of the heart and the increased blood flow, any excess of lactic acid passing into the blood would be rapidly conveyed to the heart and removed by that organ, as the heart is able to utilize lactic acid directly. The other possibility is that, owing to inactivity and diminished demands for oxygen, the muscles produce less lactic acid than they would in acute oxygen lack of a similar degree.

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Reviews.

MENTAL DEFICIENCY.

IT is almost thirty years since the first edition of Tredgold's "Mental Deficiency" appeared, and during this period considerable progress has been made in the study of amentia. The author has kept abreast of the times, and the latest edition is as complete and authoritative as it is possible to make it.[1]

This work should be of inestimable value not only to the specialist in psychiatry, but also to the general practitioner, since it covers various aspects of inheritance and environment in the ætiology of amentia, and general psychology and pathology. In fact, the author has done well to dedicate it "to all those persons of sound mind who are interested in their less fortunate fellow creatures". It should provide a wealth of interesting reading to all those who are included in this dedication.

Additions to the chapters on the nature of mental defect, on clinical examination, on mental tests and on diagnosis, and a new and informative section on the chronological development of the normal mind, all help to establish this work as the best of its kind on a subject the extent and complexity of which are only dimly realized by the average medical man. When it is appreciated that there are fourteen separate and distinct forms of mental deficiency it will be seen how extensive a study it has become. All aspects of amentia are thoroughly dealt with, including classification, physical characteristics, prognosis, treatment and training.

One cannot conclude a review of this excellent text-book without some special reference to the section on sociology, which deals with a problem of increasing importance in Australia: the problem of how to deal with mentally deficient people in order to prevent the dissemination of mental deficiency. Whatever the solution may be, whether it is segregation or sterilization of these people, or something quite different, it will also in part be a solution of those other pressing problems, crime and unemployability, and it will throw new light on the study of eugenics. The author does a valuable social service in drawing attention to these considerations and in making constructive suggestions in connexion with them. He gives due credit to the various *Mental Deficiency Acts*, the operation of which has resulted in considerable improvement in conditions in England. We might well follow suit in this country and give serious consideration to his statement that "to ignore portents of disaster until the storm is upon us is neither moral nor wise—it is merely foolish".

[1] "A Text-Book of Mental Deficiency (Amentia)", by A. F. Tredgold, M.D., F.R.C.P., F.R.S.E.; Sixth Edition; 1937. London: Baillière, Tindall and Cox. Medium 8vo, pp. 570, with illustrations. Price: 25s.

The Medical Journal of Australia

SATURDAY, SEPTEMBER 4, 1937.

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SCIENTIFIC GENEROSITY.

GENEROSITY is one of the most admirable of human qualities. Like other qualities, it is often lacking where it would naturally be expected to exist, and it can be, and often is, carried to excess. Some few persons carry their generosity so far that they impoverish themselves and later become a charge on others. Such people, however, are rare. Generosity can be manifest in the disposal of goods; it can also be of the mind. The man or woman with a generous mind thinks no evil of another and does not attribute to another unworthy motives for an altruistic action. It would probably be correct to say that women were more generous with their belongings than men, and men than women with their thoughts, but no doubt this would cause endless argument. The generous person thinks no more highly of himself than he ought to think—humility and generosity are often companions; but generosity may be made an occasion of display, and it has been said of certain persons that their generosity is a form of conceit.

Generosity is a necessity among the practitioners of medicine. That medicine is not a science, nor even a collection of sciences, is a statement that must be repeated again and again. Those who practise it would have it a science, and though we know from its nature and from the way in which it must be studied that this will never be, we should remember that the scientific ideal can be brought nearer by the cultivation of generosity of mind. That medical practitioners are generous in their relations with members of the community is never in doubt. Every practitioner has among those who rely on him for aid a number of families of slender means to whom he makes no charge for attendance; he regards this not as a duty, but as a privilege of his calling. He also, at least in most parts of Australia, gives attendance freely and gladly to those of his own and closely allied professions who seek his help. This type of generosity is what we may call hereditary; it has been instilled into every medical practitioner from his earliest years in medicine; and it will be a sorry day for the profession when payment by the State for all services rendered takes this privilege from him.

In a recent issue reference was made to professional jealousies and to their unfortunate consequences. Closely allied to jealousy is what we may call a want of scientific generosity. Professional jealousies undermine the cordial relationships that should exist between practitioners of medicine. Lack of scientific generosity, on the other hand, hampers the progress of knowledge, sometimes is a detriment to the patient's welfare, and has anything but a salutary effect on the practitioner himself. A new discovery in medicine or surgery is invariably promulgated among members of the medical profession; medical meetings, congresses and journals are used for this purpose, and there is no ground for complaint on this score. What does need attention is the attitude of some members of hospital staffs; in certain hospitals senior physicians and surgeons are alike to blame. Younger men on the staff may be known to be interested in some particular ailment, or in some new treatment that has received favourable mention overseas. There often arises an opportunity of studying the disease or the method of treatment. Seniority stands in the way. The senior knows nothing but his own method, and may

be honest enough to say that he wants to know no other. His duty should be made clear to him by the medical staff acting as a whole. Again, some member of the staff may be studying a particular disease which is rare, and which calls for intricate and difficult treatment. In the ordinary course of events it would take any man, however skilled he might be, a relatively long time to become expert in the necessary method. If certain conditions were satisfied, all work of that type should be allotted to him, so that the public might reap an early benefit. These things are not always done—scientific generosity has not yet become one of the natural qualities of the medical practitioner.

Current Comment.

CARDIAC ENLARGEMENT AFTER CORONARY OCCLUSION.

In spite of the difficulty which exists in making an accurate estimate of the size of the heart in middle-aged or elderly persons, it will be generally conceded that the ordinary methods of clinical examination can in most cases give useful results. Certainly when enlargement of the heart can be demonstrated the finding may be taken as significant, always provided that a displacement of the organ towards the left side can be excluded; in fact, an appreciation of cardiac enlargement on the part of a clinical examiner is of much greater importance than the recognition of anything which he may hear through a stethoscope. The large heart of certain types of coronary disease is very familiar, for instance, in hypertension; but what is more interesting and much more puzzling is the finding of enlargement of the heart in a patient who has had a coronary thrombosis. J. H. Palmer, using material obtained from the cardiac department of the London Hospital, remarks that coronary thrombosis is from the point of view of pathology merely an episode in coronary arteriosclerosis.[1] It is preferable to speak not of coronary thrombosis, but of coronary occlusion, since it is now known that thrombosis occurs only in a certain proportion of the cases in which a sudden or severe myocardial infarction takes place; this does not matter particularly in the present argument, which concerns the question of the cause of the large heart found in these cases. The patient may not have been under accurate observation beforehand, and, therefore, it is sometimes hard to tell whether his heart was previously enlarged. It is thus difficult to come to any definite conclusion as to the part which coronary sclerosis *per se* may play in increasing the size of the heart even in the absence of hypertension. Palmer summarizes the ideas of modern physiologists and points out that the dilatation and stretching of the muscle fibres are preludes to hypertrophy, and also that hypertrophy cannot be caused by extra work done by the heart, provided the organ is within the limit of its reserve. It is only when the heart muscle is constantly kept at full stretch with no available reserve that dilatation and subsequent hypertrophy will occur. Palmer thinks that it is possible that a moderate degree of lessening of the circulation of the coronary vessels due to sclerosis may in itself cause enlargement of the heart. However, writers on the subject seem to be of the opinion that coronary hypertrophy does not often follow coronary disease in the absence of hypertension. Parkinson and Bedford, for instance, have stated that when a really large heart is discovered in a patient who has had coronary occlusion, antecedent hypertension should be suspected.

J. Parkinson, in his Lumleian lectures last year,[1] remarks that coronary accidents prove so clearly the existence of coronary atheroma that the cases in which they occur form a good basis for the study of enlargement of the heart in coronary disease; and goes on to state that he regards the experimental and pathological evidence as inconclusive, for in the latter case it is notoriously difficult to exclude the possibility of hypertension. The series of 200 cases on which he based his opinions were also the basis of Palmer's investigation, and a very careful and thorough examination by all modern methods was made in every case. Definite enlargement of the heart was found in 64% of these patients, all of whom had suffered a proved myocardial infarction. Hypertension was outstandingly the important cause of these enlargements, no less than 82%, and in several other cases there was reason for suspecting its presence also. In a few cases bundle-branch lesions were associated with the enlargement of the heart, but without any hypertension; this, however, probably only proves the existence of coronary disease. In four cases Palmer considered that the sole cause of the enlargement of the heart was coronary sclerosis.

This careful study has given proof of what clinicians have always held; that is, that it is very common to find an enlarged heart in patients who have survived a coronary accident, and that easily the most important cause of this enlargement is hypertension. There does seem also to be reason for believing that the actual coronary disease, together with the effects of infarction of the heart muscle, can cause in itself an increase in the size of the heart in a small number of cases, the actual total figures in this series being 8·6%. It will be realized, of course, that the criterion of coronary enlargement in these cases was radiological examination; but though he must recognize the inherent limitations of bedside methods, that need not deter the

[1] *Canadian Medical Association Journal*, April, 1937.

[1] *The Lancet*, June 13 and 20, 1936.

practitioner, who has only his ears and his fingers to guide him, from reaching a conclusion in at least a good number of the cases that he sees. In other words, enlargement of the heart detected by clinical methods is a positive and definite finding, but a failure to demonstrate it by these means is quite inconclusive. This question of coronary enlargement after coronary accidents is very important because of its bearing on prognosis, but it should be pointed out finally that 36% of the patients in Palmer's series failed to show any enlargement of the heart even up to periods of three years and more. Some of this last group even survived multiple occlusion; but it would naturally be difficult or impossible to draw any conclusions from the isolated fact that the heart did not show subsequent or progressive enlargement. Nevertheless, it would be rational to prefer not to find the blood pressure again rising to an unduly high level in a patient who had had a coronary occlusion, or to find his heart enlarging, particularly if he gave evidence of a much lowered coronary reserve.

THE USE OF THE XANTHINE DRUGS IN THE RELIEF OF CARDIAC PAIN.

Recent years have seen the increasing use of numbers of drugs of the xanthine series in those forms of cardiac disease due to affection of the coronary vessels. Numbers of these, such as the various preparations of theobromine and aminophyllin, are widely advertised by reliable manufacturing chemists and extensively used by clinicians of experience. Nevertheless, as has been shown by many workers in this clinical field, it is hard to estimate the value of these drugs. Evans in his work on vasodilators, for example, found that certain of the patients on whom he made observations were too unreliable to be included in his results. Whether some of the experimental evidence as to the capacity of certain drugs to cause vasodilatation can be relied upon as representing what happens in human practice is open to question. But it is easier to take a simply observed symptom such as pain and to make clinical observations on various drugs used for its relief.

H. Gold, N. T. Kwit and H. Otto have made some useful observations on the treatment of cardiac pain by some of the xanthine drugs, and record their results in a recent paper.[1] The New York Heart Association has laid down certain criteria of arteriosclerotic heart disease with cardiac pain, and these were used in collecting the cases used for observation in this series. One hundred ambulant patients were selected as being suitable for the inquiry. None of these suffered from congestive failure, but in every case effort angina was a symptom, varying in degree from a mild substernal discomfort to excruciating pain precluding any degree of activity on the part of the patients. The majority of these patients were not engaged in work, so that the conditions of study were well controlled. At the beginning of the observations an attempt was made to distinguish between patients who could discriminate between a tablet of glyceryl trinitrate and a placebo and those who could detect no difference in the result during an attack of pain. It was found, however, that this condition was too severe to be of practical value, and this restriction was abandoned. It may be remarked that this difficulty akin to that encountered by Evans, as mentioned above, illustrates the balanced judgement which is necessary in presenting clinical observations, particularly as regards the results of treatment. The drugs used in the investigation were theobromine, aminophyllin (theophyllin with ethylenediamine), the total daily dosage being 15 to 60 grains of the former, and 9 to 12 grains of the latter. These correspond to doses of a reasonably high magnitude, and their administration was continued for a number of weeks, sometimes for some months. Courses of treatment were alternated with the use of a placebo in order to check the accuracy of the patients' observations, and due care was taken to control the experiments so as not to suggest to the patients the expected result. The most arduous part of the work proved to be the securing of the data, and it was found that much more time was required than could be afforded by the usual routine inquiry of the hospital clinic. An effort was made to classify the degree of pain from which the patients suffered, and observations of blood pressure were also made. The authors found that a number of factors might influence the abatement of pain. Included in these were spontaneous variations, weather change, change in occupation, in diet or in domestic affairs, emotional stress, and even a change in medical advice. The importance of recognizing such factors in the evaluation of treatment will be substantiated by all those who have an adequate clinical experience. The outcome of the authors' investigations was rather disappointing in one sense, for no evidence could be found that the xanthine drugs exert any specific action of value in the routine treatment of cardiac pain. No appreciable effect on the blood pressure was noted. This work appears to have been carefully carried out, and, therefore, the conclusions should be of value, even though they are rather destructive. It cannot be said that the xanthine drugs are entirely without value: they appear to have some diuretic effect, and may even assist the coronary circulation a little, though, in the light of recent work, this is extremely doubtful. But they apparently are not comparable with glyceryl trinitrate for the relief of cardiac pain, provided that this latter drug is administered correctly, that is, by being placed in the mouth without being swallowed. The wise clinician will not forget also that there are many other methods of preventing the onset of pain of an anginal nature, and, indeed, the general advice given to the patient is likely to be of much greater value to him than any drugs.

[1] *The Journal of the American Medical Association*, June 26, 1937.

Abstracts from Current Medical Literature.

OPHTHALMOLOGY.

Accidental Freezing of the Eye by Sulphur Dioxide.

C. P. CLARK (*American Journal of Ophthalmology*, October, 1936) describes two cases of freezing of the anterior portion of the eye by the bursting of a sulphur dioxide unit of a refrigerator. The lids were swollen and firm, and the cornea and conjunctiva had the appearance of hard-boiled egg albumen. The author says that in such cases the eye should be washed out with cold water, and this should be followed by iced compresses, local anæsthesia, the instillation of atropine solution, and the application of an antiseptic ointment. Usually no damage results.

New Operation for Glaucoma under Direct Magnification.

O. BARKAN (*American Journal of Ophthalmology*, November, 1936), from biomicroscopic studies, decided that the trabeculum, or inner wall of Schlemm's canal, was the seat of blockage in the filtration of ocular fluids. He also observed that this impervious trabeculum was untouched by any of the present-day operations for glaucoma, such as cyclodialysis or trephining. The first seven patients were operated upon by inserting the knife outside the temporal limbus and slowly sweeping it round the lower and inner circumference of the limbus. The operation was performed blindly, and damage was easily possible. However, in all cases but one Schlemm's canal was struck and opened over a sufficient extent to reduce pressure. The author has developed a surgical contact glass which enables him to operate on Schlemm's canal with this region in full view and magnification. Illumination is provided by a hand slit-lamp held temporally, combined with a strong overhead lamp. The operator, wearing a head loupe, pierces the temporal limbus with a specially designed knife, which he passes across the chamber and then deliberately inserts into the trabeculum, which is in full view on the other side of the anterior chamber. The dark trabecular pigment band is sufficiently distinct to act as a guide. The incision is continued downwards, and Schlemm's canal is opened through one-fourth or one-third of its extent. Eserine is used before and after operation.

Operation for Entropion.

A. BUSACCA (*Archives of Ophthalmology*, November, 1936) describes a method of operating on entropion resulting from trachoma. The skin of the upper lid is incised in a line parallel to the free border and five millimetres above it. The skin is freed upwards to the height of the superior margin of the tarsus, and at this level an incision of the muscle is made down to the tarsus. The lower skin flap is then freed and the muscle incised. The muscular bundles between the two incisions are removed by scissors. A linear incision is made on the tarsus, five to eight millimetres from the margin of the lid, care being taken not to reach the conjunctiva. Then thin slices of the tarsus are removed with the knife from the cilia up to the tarsal incision. The inferior lip of the wound is sutured to the superior side of the tarsal flap. The superior lip of the wound is left alone. Bandaging is important, to promote contact for twenty-four hours.

Retinal Allergy.

J. S. PLUMER (*Archives of Ophthalmology*, March, 1937) describes the case of a physician, aged thirty-five years, who complained of poor vision of recent origin in the left eye. There were slight macular changes. After recovery he had a relapse, and then it occurred to him that both attacks followed the eating of peanuts. He was allergic also to chicken meat and various pollens.

Chorioideremia.

A. J. BEDELL (*Archives of Ophthalmology*, March, 1937) reviews the literature dealing with chorioideremia since the report of Mauthner's case in 1871, and reports five new cases. The disease is characterized by poor vision and night blindness and constriction of the visual fields. Several members of a family may be affected. The greater part of the fundus appears of a greyish white, with scattered pigment spots. The ordinary red reflex of the choroid is limited to a small patch in the macular region and around the disk. Some isolated chorioidal vessels may be seen, and in the peripheral part of the visible fundus there is a faint red tinge. The visual field is limited to 10° or less from the centre, or there may be some peripheral ring. The retinal vessels cross the white colour of the sclera. The optic nerve may be normal in appearance, but the vessels are smaller than normal. The white fundus reflex distinguishes the condition from *retinitis pigmentosa*. The author defines chorioideremia as a condition in which the choroid disappears; first the small vessels disappear, and then the larger ones become narrow and finally melt away. The condition is bilateral. With one exception all the patients were males.

Cyclic Paralysis of the Oculomotor Nerve.

A. M. HICKS AND G. N. HOSFORD (*Archives of Ophthalmology*, February, 1937) review the literature of the thirty-five cases of cyclic paralysis of the oculomotor nerve reported, and contribute two cases of their own. A girl, aged eighteen years, stated that her left eye had always been small and the vision poor. The pupil did not react to light or accommodation, but exhibited alternating phases of miosis and mydriasis. There was an increase of from two to three diopters in the miotic phase. None of the external muscles took part in the cyclic phenomenon. The spastic pupil contracted to two millimetres and relaxed to six millimetres. The complete cycle lasted from twenty to thirty seconds. The second patient, a girl aged twenty years, was referred for surgical correction of marked divergence of the right eye due to congenital paralysis of the oculomotor nerve. The right lid drooped so that the palpebral fissure was only three millimetres wide; the lid could not be voluntarily elevated. There was proptosis of the right eyeball, and it was grossly abducted and fixed in this position. Viewed two minutes later, the picture had changed. The upper lid was raised like the left. The pupil was constricted to two millimetres. There was a little inward movement on voluntary convergence. The refractive error changed from +3 to −0·5. The cycle required from two to three and a half minutes. In the absence of anatomical evidence the causation is theoretical.

Epiphora.

P. CHALMERS JAMESON (*Archives of Ophthalmology*, February, 1937) describes an operation for subconjunctival section of the ductules of the lachrymal gland in chronic epiphora. An opening is made on the conjunctival surface of the lid, adjacent to and slightly below the outer canthus. The upper lid is then inverted so that the fornix is put on a stretch. Scissors are used to separate the conjunctiva from all the basic tissues of the fornix, for a distance of the outer two-thirds. The points of the scissors are visible through the conjunctiva; if not, they are too deep and dangerous to the levator muscle of the lid. The bulbar conjunctiva adjacent to the fornix is then put on a stretch and the field of separation is gone over again, the operator making sure that the division of the fornix and the conjunctiva from their basic tissues is complete. If this separation is complete, every ductule has been sectioned. The author found no œdema in the orbital tissues after operation. The cure is not manifest for some days, that is, until the wound is healed.

OTO-RHINO-LARYNGOLOGY.

The Development of the Human Palatine Tonsil.

W. L. MINEAR, L. B. AREY AND J. T. MILTON (*Archives of Otolaryngology*, May, 1937) describe and discuss the life history of the crypt system in the human palatine tonsils as deter-

mined from a study of serial sections and wax reconstructions of significant stages, from the first buddings of prenatal life to the atrophic tonsil of old age. They conclude that the crypts of the human palatine tonsil begin to appear during the third fœtal month as solid ingrowths from the epithelial wall of the tonsillar fossa. Subsequently these epithelial processes grow and branch and become canalized, although the end of such progressive development is not reached until childhood. The formation of a lumen usually takes place first in the distal, most rapidly growing part of an epithelial ingrowth. However, simultaneous formation of the proximal and distal portions of the lumen occurs also. A first phase in the development of the crypt system is characterized by a peculiarity of growth, owing to which many of the epithelial ingrowths form epithelial vesicles (cystic crypts). The majority of these epithelial vesicles, attached to the permanent crypts by narrow necks (most necks are solid, but some have lumina), undergo progressive degeneration and disappear shortly after birth. However, it is possible that some persist as the residual vesicles (cysts) of childhood and adult life. A second phase in the growth of the crypt system, which also begins in early prenatal months, is marked by the appearance of the new first-order crypts, by further growth of similar crypts (straight or curved plate-like type) of the first and second order, which escape destruction during the first phase, and by the formation of many new second- to fifth-order crypts, which increase in number gradually up to the time when the full quota is obtained (some during early childhood). Although the maximum number of crypts is reached during childhood, these later elongate and enlarge by interstitial growth, to form the definite crypt system. In the series of models obtained by the authors, the number of first-order crypts remains relatively constant throughout childhood and even until the onset of tonsillar senescence. A greater variety of shapes is found accompanying the increase of number and complexity of the crypts than occurs in the earlier crypt systems. The shape of the original epithelial ingrowth is the principal factor that determines the shape of the crypt. Some crypts are bud-like, some irregularly cylindrical, and some long, narrow and sinuous. But the curved or flat plate-like type is predominant in number and size. Many of the large first- and second-order crypts have constricted necks. Anastomosing crypts are of great rarity and have been demonstrated for the first time. The size and complexity of most crypts in the superior half of the tonsil are greater than in the inferior half. This domination persists from fœtal life, at which time the formation of the superior part of the tonsil occurs in advance of the inferior portion. From the beginning of the development of crypts until childhood the crypts of the inferior half of the tonsil are relatively short and small. The completion of growth, inferiorly, so that this region is filled in equally with the superior half, is the most outstanding advance of the final developmental period, which produces the definite tonsil. The final phase in the life history of the adult crypt system is marked by a progressive atrophy and degeneration, reminiscent of the late prenatal and early postnatal period. The less complex portion of the crypt system of the inferior half of the tonsil is not only the last to attain full growth, but the first to degenerate. Again, vesicles and cysts appear as by-products and number and order of the crypts are reduced. Atrophy of lymphoid tissue and compensatory formation of fibrous tissue accompany the degeneration of the crypt system. Ducts of the peritonsillar mucous glands establish themselves before the crypt system has attained any prominence. This explains why the ducts are so rarely found emptying into crypts, and then always near the mouth. Connexion with crypts is the result of secondary incorporation. Dilated mouths of ducts surrounded by lymphoid tissue sometimes simulate simple crypts into which ducts empty; but these should not be confused with true crypts. The approximate area of the epithelial lining of the adult crypt system of one tonsil was calculated to be 296 square centimetres (46 square inches), whereas the exposed surface area of an entire pharynx was only 45 square centimetres (seven square inches). Any tendency to empty the tonsillar crypts through natural or artificial means must necessarily be inefficient, owing to anatomical constrictions and the tendency of the contents of a complex convergent system to become impacted at the bottle-neck region of the main crypt. Such plugging is further enhanced by the circumstance that the main drainage channel is often smaller than its tributaries.

Bronchiectasis in Children.

GEORGE B. FERGUSON (*Archives of Otolaryngology*, April, 1937) discusses bronchiectasis in children, making special reference to prevention. He concludes that mechanical obstruction is one of the most important factors in the production of bronchiectasis. Since in many cases bronchiectasis originates during or shortly after the acute infectious illnesses of childhood, special watchfulness is necessary when signs of pulmonary lesions are present. Bronchoscopic examination, as an aid to diagnosis, is indicated for children with chronic cough or for those who have repeated pulmonary infections, provided pulmonary tuberculosis has been excluded. In many instances bronchiectasis could be prevented by removal of the source of mechanical obstruction, thus aiding aeration and drainage of the lung. Bronchoscopic aspiration is an effective means of providing and maintaining free pulmonary drainage. When such aspiration is combined with suitable general measures and appropriate care of the nose and throat, bronchiectasis in its early stages may be cured. In the late stages many patients may be so improved as to be able to lead normal lives if they are somewhat careful.

Bronchoscopy in Broncho-Pulmonary Suppuration.

A. SOULAS (*The Journal of Laryngology and Otology*, April, 1937) discusses the mechanism and results of treatment by bronchoscopy in broncho-pulmonary suppuration. The cure of bronchiectasis treated by bronchoscopy is rare (15%), and in general results only in the case of recent bronchiectasis following pulmonary abscess or bronchopneumonia, or in the presence of a foreign body. In all other cases the author obtained only a symptomatic improvement, sometimes remarkable, with even a partial restoration to the normal state ("social cures", 28%). Often only simple improvement is obtained (52%), necessitating repeated treatment over a long period. In general the author repeats bronchoscopic treatment twice, seven or even eight times a year. It is for this reason that in many cases, if the broncho-pleuro-mediastinal fibrosis or the bilateral character of the lesions is not a contraindication, the new thoracic surgery must be employed.

Ménière's Disease.

DONALD MUNRO (*The New England Journal of Medicine*, April 1, 1937), in a paper dealing with the surgical treatment of certain repeated explosive attacks of vertigo occurring in the absence of any demonstrable ætiology (Ménière's disease), gives a report of fourteen cases of this and other types of aural vertigo, and includes one case in which both vestibular nerves were involved. He concludes that the diagnostic terms "aural vertigo" and "Ménière's disease" are neither interchangeable nor synonymous. Aural vertigo predicates a demonstrable cause for the dizziness, while the term "Ménière's disease" is applicable at present only to those cases of vertigo that appear to have an aural origin, but for which no cause can be found. Ménière's disease is curable in nearly 100% of cases by division in the posterior fossa of the skull of either the entire eighth cranial nerve or its vestibular portion alone. There is some evidence to show that certain patients with aural vertigo may also be helped by this operation. The ætiology and pathology of Ménière's disease are unknown at present. The operative division of the vestibular portion of the eighth cranial nerve through a unilateral sub-occipital craniotomy is described and its wider use advocated.

British Medical Association News.

SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held on May 27, 1937, at the Robert H. Todd Assembly Hall, British Medical Association House, 135, Macquarie Street, Sydney, DR. LINDSAY A. DEY, the President, in the chair.

DR. B. T. EDYE read a paper entitled: "Fractures of the Spine" (see page 371).

DR. D. J. GLISSAN read a paper entitled: "Treatment of Spinal Fractures" (see page 376).

DR. STACY said that his interest in the subject under discussion dated from the appearance of an article by Watson Jones in *The British Medical Journal* in 1931. He (Dr. Stacy) had adopted the method advocated when he was called upon to deal with a fracture of the spine which had occurred from six to eight weeks prior to his seeing the patient. Hyperextension, however, had no effect. In February, 1932, he had occasion to see a Chinese who had sustained a fracture of the spine three days previously. He gave the patient 0·015 gramme of morphine before putting him into a position with the table supporting the shoulders raised twenty-one inches above the level of the table supporting the thighs. Several months later he had another patient whom he treated in the same way; this fracture was eighteen days old. The fractures in both these cases were successfully reduced by hyperextension and the patients were walking in ten days; there had been no cord involvement. Dr. Storey had commented that he himself would be afraid that the patient would have a severe fall if the lower stool moved, and Dr. Stacy felt that this criticism was just. It was important that the stool or table should be securely fixed. Dr. Stacy said that he had had experience of hyperextension in only three instances of spinal fracture, all occurring in the dorso-lumbar region. He had seen in consultation a patient who had obvious cord involvement from antero-posterior and lateral fracture-dislocation; no attempt had been made at replacement, and he died a little later. Watson Jones later, in a personal communication, said that the correction of the antero-posterior displacement was the more important as regards cord involvement. Referring to the question of transporting persons who had been injured in accidents, and who might have sustained spinal fractures although no symptoms were present to show whether this was so or not, Dr. Stacy said that the giving of a general order that all injured persons suspected of having fractured spine should be transported only in the prone position would be attended with great difficulty and would in some circumstances be dangerous. Watson Jones apparently found it impossible to convince some of the English authorities that ambulance officers should be so instructed, and, indeed, it was throwing a great deal of responsibility on such officers; but it should be remembered that it was very easy by faulty transport (with consequent increase of the flexion) to change a condition in which there was no injury of the spinal cord into one in which the cord was injured. This was particularly true of fractures in the dorsal region owing to the smaller space in the spinal canal; hence he would like to see the method of transportation in the prone position more generally adopted. Dr. Stacy then expressed his gratitude to Dr. Edye and Dr. Glissan for their very interesting papers, and also to Dr. Lovell, who had very kindly prepared the graphs.

DR. J. C. BELL ALLEN said that lateral crushing could take place as well as antero-posterior, and the scoliosis resulting from such a crushing was very difficult to correct. It was also very hard to get muscular relaxation. Dr. Allen said that he would be glad of advice as to the best way of dealing with lateral crushing; it was possible that hanging the patient in a special frame might effect the necessary reduction of the fracture. He showed X ray photographs of a patient in whom lateral crushing had occurred. With regard to the ordinary fractures of the transverse processes of the spine, Dr. Allen said that he was of the opinion that the less notice that was taken the better, on account of patients' natural horror of "a broken back". Rest in bed with massage and no plaster cast he considered to be the best treatment for patients with such injuries. If a plaster was put on they would never cease to complain.

DR. LYLE BUCHANAN thanked Dr. Edye and Dr. Glissan for their excellent papers. He emphasized the fact that in dealing with fractures of the spine, time was the essence of the contract. He said that he had had experience of five injuries of this nature. Two were simple crush fractures, which were easily reduced and gave excellent results. Two other fractures did not respond so satisfactorily to treatment. One of these, a fracture-dislocation in the lumbar region, was irreducible by the method outlined in Watson Jones's book. Elongation of the spine was needed, so the patient was finally suspended by the heels under local anæsthesia, and reduction occurred. In the case of the fifth patient, any attempt to reduce the fracture by simple posturing was useless. Elongation in a Glissan sling was tried, with no effect. The surgeon was handicapped in the use of this instrument by having to exert a pull of from seventy to eighty pounds. Dr. Buchanan then demonstrated his universal splint, which he held was suitable for treatment of these injuries. It was designed to give control of the patient's head, neck and shoulders, at the same time leaving the surgeon free for the actual manipulation.

DR. GEORGE BELL congratulated the speakers and paid a tribute to Dr. Lovell for constructing the graphs. He asked Dr. Edye what he considered to be the best method of treatment for retention of urine when it occurred in connexion with spinal fractures. During the Great War it had been a common practice to pass a catheter once or twice a day and irrigate the bladder. Suprapubic drainage was another method which was sometimes used. Expression of the urine had also been advocated. Of late years the method in use at Sydney Hospital had been the indwelling catheter. This was tied in, and the bladder was washed out twice a day. The catheter was changed every second day and all apparatus was boiled or sterilized once or perhaps twice a day. This method was better than that employed during the war. Dr. Bell said that he was always reluctant to perform a laminectomy except in cases in which the *cauda equina* was involved. Watson Jones's procedure had great advantages. It was simple, and thus was within the range of the practitioner's ability when simple apparatus was at hand. Speaking of severe injuries, Dr. Bell wondered whether there was a risk of causing further injury by applying this method too roughly. Supposing the patient to have suffered a spinal fracture in which the anterior spinal ligament was partly torn through, additional damage might easily be done by too severe manipulation. He mentioned one patient suffering from fracture of the spine in the cervical region who had no obvious neural injury, but when the nurse attending to him moved his head slightly the man immediately became paralysed. Great advances had been made in diagnosis with the help of radiographers. Before good lateral views of the vertebræ were obtainable, fractures of this type were often missed. Dr. Bell said that he knew of one case that had been missed because no good lateral view had been obtained.

DR. J. C. STOREY expressed his gratitude to the speakers and thanked them sincerely for their excellent papers. One aspect of the subject had been missed, he thought. Dr. Edye's figures were probably not an accurate indication of the number of fractures of the spine. There was no information concerning the incidence of this type of injury in the whole community. The saddest injuries were those to healthy young people, because these could be prevented if the public would only learn that they should always go into strange water feet first. They should be educated in these matters through the surf life-savers and other such organizations. Various surf tricks were very silly. Speaking of laminectomy, Dr. Storey said that he knew of a sad case. The patient had complete paralysis due

to a lesion of the cervical cord, and he had been asked to operate. He had demurred, but had at last consented. The patient died very early in the operation. Later he was asked to perform laminectomy on a patient with a similar condition, but absolutely refused. He had used Böhler's technique a few times. In his present frame of mind, Dr. Storey said that when he came in contact with a patient who had sustained a fracture-dislocation in the cervical region with immediate paralysis, he though it best to send for the patient's religious adviser and let his end be peaceful. He spoke of a healthy young man who had complained of pain after having some time previously held a large slab of stone. He had not made any jerking movements, but had steadied the slab on the end of a lorry. An X ray photograph was taken, and it was found that the spine of the first dorsal vertebra had been torn off. The patient who had sustained a fracture of a transverse process should not be told that he had a fractured spine, but that he had torn some bony processes to which the muscles were attached, and that he would recover. He should not be put in a plaster jacket. This was a very important point, and much could be done with these patients if such an attitude was carefully fostered. It quite often happened that if a patient was told he had a "broken back" he became a chronic invalid. Referring to the difficulty of stransporting injured persons, Dr. Storey said that it would be far too much to expect the ambulance men to recognize a fracture of the spine in all cases; quite often the patient was not paralysed. He thanked the speakers again for the interesting papers they had presented and said that it was most disappointing that there were so few members at the meeting to see how much work had gone into their preparation.

Dr. Glissan, in reply, thanked those who had spoken in criticism and eulogy of the papers. He said that he had found Dr. Edye's paper very refreshing and thought Dr. Lovell's graphs excellent. He would like to draw attention to a curious point that had occurred to him when listening to Dr. Edye, who had described the case of a man who had injured his spine in a sulky accident and had been able to walk about immediately afterwards. He went home and got into bed and immediately became paralysed. The question to be determined was, was it the walking about or the lying down that did the final damage? Was it not possible that the recumbent position on a sagging bed had converted a moderate into an acute crush fracture and produced spinal compression? Thus again the question of transport in spinal fractures was raised. He was not in favour of promulgating rigid general orders about transport; such an action might be liable to have very serious results. The case which Dr. Allen had described was interesting and unusual; the acute lateral deviation of the spine was likely to prove a handicap later in the patient's career. The rationale of the treatment laid down by Watson Jones was that the crush should be opened up in the direction in which it had been produced. He would be inclined to place such a patient in a lateral position at the outset. He had not seen a lateral skiagram, however, and would not like to venture any further opinion on this case. Dr. Glissan endorsed the remarks about treating lightly fractures of the transverse processes of the spine. The degree of disability associated with any fracture was closely related to the function of the bone concerned. In the case of the transverse processes, their function was solely to act as points of attachment to muscles that controlled some of the movements of the spine, and the degree of disability therefore would depend on the extent to which such muscles were deprived of their action, and further, on the extent to which they could reattach themselves; in any case, this degree of disability was likely to be very slight. It was important to watch the patient's mental attitude in cases of spinal fracture and to be determinedly hopeful. Dr. Buchanan's remarks had really centred round the question of treatment of dislocation in the cervical region; this was always a difficult problem, but it had been included in the scope of his paper. Somebody had mentioned Glisson's sling, and he would like to take the opportunity, not without regret, certainly, to dissociate himself from any responsibility for the genesis of this piece of apparatus. He was moved to make these remarks in self-defence, for it was quite a frequent occurrence for various surgical instrument makers to telephone him for help in attending to a telegraphic order for a Glisson's sling received from a country practitioner.

Dr. Edye, in reply, thanked the audience for their kind remarks. He said that Dr. Storey was quite right; a great deal of work had gone into the papers. He had intended to say something about patients with cord injuries, but time had not permitted. Referring to the treatment of retention of urine, he said that the indwelling catheter, the method in use at Sydney Hospital, was considered the best. He was doubtful, however, as to how long the condition should be allowed to continue. The question was: Should the bladder be encouraged to achieve automatic action? It was uncertain whether the bladder was able to empty itself completely under these conditions, and it was most important that there should be no residual urine. If there was, infection became impossible to prevent. He himself had had no experience of suprapubic drainage. It might be a good procedure in some instances. Speaking of the value of a lateral X ray view of spinal fractures, Dr. Edye spoke of a patient who had fallen out of a tree. The X ray picture showed no fracture of the spine. A lateral view, however, did show it. With regard to surf accidents, Dr. Edye said that he had heard recently of a young married woman with three small children who had been tossed up while at the beach. She had landed on her head, sustained a fracture in the cervical region and died. This was another indication of the foolishness of such forms of sport.

A MEETING of the New South Wales Branch of the British Medical Association was held at the Royal Alexandra Hospital for Children, Sydney, on April 22, 1937. The meeting took the form of a series of demonstrations by members of the honorary staff.

Rheumatoid Arthritis.

DR. EDGAR STEPHEN showed four patients suffering from rheumatoid arthritis who had been treated with "Solganal B. Oleosum". They had all improved greatly. He drew attention to the high red cell sedimentation rate prevailing in this disease, a rate much higher than that encountered in acute rheumatism. He gave the dosage used in these cases, together with the ages of the patients and the sedimentation rates. No unfavourable reactions or skin rashes had been noted. He said that the method of estimating the sedimentation rate in use at the Children's Hospital gave, for children in normal health, a reading of three to ten millimetres in the first hour and a total of twenty millimetres by the end of the second hour.

Pink Disease.

Dr. Stephen then showed a girl, aged sixteen months, suffering from pink disease. The child had a history of illness of one month's duration, with increasing irritability, loss of weight, loss of appetite, photophobia and vomiting. The hands and feet were cold and red. On examination the child was seen to be intensely miserable; photophobia was present, as well as severe hypotonia; gross loss of weight was apparent. The pulse rate was 120 to 130 per minute. No scaling nor rash was present; no abnormality could be detected in the heart or lungs. The hands and feet were very red. The child was cutting teeth and the mouth hung open.

Rickets.

Dr. Stephen then showed a boy, aged nineteen months, who had been admitted to hospital suffering from acute bronchitis and convulsions. The condition had rapidly subsided in hospital. Rhachitic changes were apparent; the ribs were splayed, the costal angle was widened, the ligaments were lax and the central incisors were notched. Hypotonia was present and Harrison's sulcus was obvious.

Lipoid Nephrosis.

Dr. Stephen next showed a girl, aged three years, suffering from lipoid nephrosis, who had been admitted to hospital on April 3, 1937. At the time of admission there was pronounced generalized œdema; the tonsils were enlarged and injected; the urine contained a heavy cloud of albumin. The blood urea content was 19 milligrammes per 100 cubic centimetres of blood; the cholesterol content was 336 milligrammes per 100 cubic centimetres. The patient was given two ounces of grated apple every two hours for three days. The œdema had disappeared, and she was now taking a high protein diet without milk. The child had previously had acute rheumatism, and at the time of the meeting she had a musical mitral systolic murmur. Dr. Stephen said that in this case, as well as in several others, the diet of grated apple had been followed by the disappearance of the œdema and an improvement in the general condition.

Rheumatic Fever and Chorea.

Dr. Stephen also showed patients and charts of patients suffering from rheumatic fever and chorea. In these cases the red cell sedimentation rates had provided indications for permitting increases in activity and had been of value in estimating the condition of the heart.

Chorea and Rheumatic Carditis with Hæmaturia.

DR. M. J. PLOMLEY showed a girl, aged nine years, who had been in the hospital in 1935 suffering from acute rheumatism. She was admitted to hospital on January 4, 1937, with a history of nervousness, clumsiness, and difficulty in speaking, of four months' duration. Well-marked choreiform movements of the arms, hands and feet were present. The apex beat was heard in the fifth intercostal space just outside the mid-clavicular line and systolic and diastolic apical murmurs were audible.

By February 12 the choreiform movements had disappeared. The apex beat was to be felt in the fifth intercostal space outside the mid-clavicular line, and a systolic murmur only was heard. On March 8 the child complained of pain and tenderness of the right knee. The next day pronounced hæmaturia appeared and the child was very ill. On March 12 the apex beat was felt 3·75 centimetres (1½ inches) outside the nipple line in the fifth intercostal space. The heart rhythm was irregularly irregular; there was a pulse deficit of thirty beats and systolic and diastolic murmurs were present. On March 15 the irregularity had completely disappeared. By March 22 the child was much better; the apex beat was heard in the fourth intercostal space 1·25 centimetres (half an inch) outside the mid-clavicular line, and diastolic and systolic murmurs were heard. On April 17 the child was very well and was having teeth removed; diastolic and systolic murmurs were heard. The blood gave no reaction to the Wassermann test.

Congenital Heart Disease.

Dr. Plomley also showed a boy, aged three years, suffering from congenital heart disease. He had been admitted to hospital on March 5, 1937, in a very breathless and cyanosed condition. On examination the child was seen to be distressed and breathless. The apex beat was in the sixth intercostal space in the mid-axillary line; a systolic murmur, loudest at the apex, was audible over both sides of the chest. There were signs of consolidation at the base of the right lung. The liver border was palpable 2·5 centimetres (one inch) below the umbilicus. After rest and several doses of digitalis the child was discharged from hospital on March 20 not distressed and quite cheerful.

On April 8 he was readmitted to hospital. He was breathless, distressed and cyanosed, and the legs, sacrum and face were œdematous. X ray examination on March 8 revealed uniform enlargement of the cardiac shadow. Increased mottling was present in both lungs, particularly the right lung; this might have been secondary to the cardiac condition or it might have been pneumonic. A futher X ray examination on March 15 revealed that the heart was enlarged as before, that vascular congestion was present in the lungs, and that there was a small area of central consolidation at the lower end of the right hilum.

Rheumatic Carditis.

Dr. Plomley's next patient was a boy, aged seven years, suffering from rheumatic carditis. He had been admitted to hospital on February 25, 1937, with a history of pains in the wrists and knees and of having had a sore throat six weeks previously, when he had spent one week only in bed. At the time of admission there was pain in the hands. The child was very pale; the apex beat was felt in the fifth intercostal space, half an inch outside the mid-clavicular line; the heart sounds were of very poor tone and apical systolic and diastolic murmurs were heard. The tonsils were not very inflamed. On March 15 it was noted that the cervical lymph glands were enlarged and the tonsils acutely inflamed. Very loud systolic and diastolic murmurs were heard and the apex beat was in the fifth intercostal space outside the nipple line. X ray examination on that day revealed considerable dilatation of the heart. Both sides were enlarged and there was pronounced venous congestion of both lungs. Blood examination revealed a fall in the hæmoglobin value and in the number of leucocytes.

DR. R. J. TAYLOR showed a girl, aged seven years, who was suffering from rheumatic pancarditis. She had been in hospital in 1935 suffering from acute rheumatism, and had been readmitted to hospital in March, 1936, with a recurrence of the condition. At the time of her second admission to hospital the apex beat was in the fifth left intercostal space in the nipple line and a harsh systolic murmur was audible at the mitral area, propagated to the axilla. The joints affected during the second attack were the ankles, the interphalangeal joint of the right hallux and the left knee joint; abdominal pain was also present. The patient was discharged on May 23, 1936, but was readmitted to hospital on June 4, 1936, complaining of pain in both knees, swollen ankles and abdominal pain. On examination the apex beat was palpable in the eighth left intercostal space, 8·75 centimetres (3½ inches) from the mid-line; it was diffuse and forcible, with a well-marked thrill. Auscultation revealed harsh presystolic and systolic murmurs all over the precordial and left axillary areas, being loudest in the mitral area. The lower border of the liver was palpable 2·5 centimetres (one inch) below the costal margin. On June 11, 1936, the child was found to be suffering from bronchopneumonia.

On April 21, 1937, the apex beat was in the eighth left intercostal space, 10·0 centimetres (four inches) from the mid-line, and was diffuse and heaving. There was a presystolic thrill. On auscultation harsh presystolic and systolic murmurs were heard, with a diastolic murmur, which was loudest in the mitral area and base, but was heard over almost the whole chest. The apex beat did not appear to move when the child was turned. The lower level of the liver was at the umbilicus. There was some free fluid in the abdomen, but no œdema of the sacrum or ankles, nor were the lungs congested. *Paracentesis abdominis* was performed on February 22, 1937. X ray examination revealed enormous dilatation of the heart, with vascular congestion of the lungs. The possibility of effusion into the pericardial sac, as well as dilatation, was also suggested. X ray screening carried out on April 20, 1937, revealed that the heart did not appear to be fixed to the thoracic wall.

Myopathy Treated with Ephedrin and Potassium Chloride.

Dr. Taylor also showed three patients suffering from myopathy who were being treated with ephedrin and potassium choride.

The first patient, a boy, aged ten years, was a typical example of pseudo-hypertrophic muscular dystrophy of rather advanced degree. His first symptoms appeared at the age of five years. There was no familial history of myopathy. Before treatment was begun two months previously, the child could not stand nor walk, nor could

he raise his trunk from the ground when placed supine. He was given 0·03 gramme (half a grain) of ephedrin sulphate and 1·8 grammes (thirty grains) of potassium chloride, three times a day. Within a fortnight he had shown some improvement. At the time of the meeting, after being helped from his chair, he could stand without support; he could walk from room to room, occasionally touching the wall to maintain his balance, and he could raise himself to the sitting position after having been placed flat on the floor.

Dr. Taylor's next patient, a girl, aged seven years, suffered from a mixed form of the disease. Her first symptoms had appeared at the age of four years. There was no familial history. The child had an expressionless face, double ptosis, waddling gait and pronounced lordosis, and before the commencement of treatment four months previously she could not go up or down stairs, she could not walk more than fifty yards, and, when placed in the supine position, could get to her feet only by going through the series of movements classically associated with the muscular dystrophies. She was given 0·015 gramme (a quarter of a grain) of ephedrin sulphate and 1·8 grammes (thirty grains) of potassium chloride three times a day. Improvement was noticed very soon. At the time of the meeting she could go up and down stairs, could walk two or three miles, and could raise herself to her feet, in clumsy fashion, but almost as quickly as a normal child.

Dr. Taylor's third patient was atypical. He was a boy, aged six years, who had always been unsteady on his feet, but who had become much more unsteady at the age of four years. All his muscles were poorly developed; the reflexes were normal. To reach the standing from the lying position, he adopted the characteristic myopathic manœuvres. When an attempt was made to lift him up with a hand in each axilla he tended to slip through the grasp. He was given the same treatment as the second patient, and later the dosage of ephedrin sulphate was raised to 0·02 gramme (a third of a grain) three times a day. He had given practically no response.

Hemichorea.

Dr. Taylor's next patient was a girl, aged twelve years, who was suffering from hemichorea. Five years previously she had sustained a fracture of the left side of the skull. The child had been sick for one week prior to her admission to hospital; there had been loss of power and twitching of the right arm, the speech had been thick, and she dragged her right leg. The patient was a normal, bright child. There was a slight right facial paresis and the tongue deviated to the right. Involuntary, purposeless movements of the right arm and leg were present. The sensory nerves were normal. Examination of the reflexes revealed that the pupils were equal and reacted to light and accommodation, that the knee jerks were present and equal, that the plantar responses were both flexor, and that the abdominal reflexes were equal. X ray examination of the skull revealed no abnormality. The ocular fundi were normal. The red cell sedimentation rate was nine millimetres at the end of the first hour (normal, three to ten millimetres) and sixteen millimetres after two hours (normal, twenty millimetres). At the time of the meeting the facial paresis had disappeared and the movements were much less; but the tongue continued to deviate slightly to the right.

Lead Poisoning.

DR. MARGARET HARPER showed a boy, aged six years, who was suffering from lead poisoning. The child had been admitted to hospital on February 4, 1937, and at that time weighed 12·6 kilograms (two stone). The family history was interesting; the mother had been living for years in a cottage behind which was a lead smelting works; both mother and father were alive and well and also the two elder boys. There was no history of tuberculosis.

The child had been in the hospital suffering from marasmus at the age of two years; he had been in the Royal Prince Alfred Hospital in 1936 with broncho-pneumonia. The mother stated that the child had always been thin, but had lost 1·8 kilograms (four pounds) weight during the fortnight prior to his admission to hospital and had been complaining of abdominal pain. He was irritable and bad-tempered. The bowels were open regularly and no vomiting, cough or night-sweats had occurred.

On examination the child was seen to be very thin and wasted; he was of only moderate intelligence; the tongue was furred, the fauces were clear and the tonsils small. The abdomen was concave and very lax. There was a "blue line" on the upper alveolar margin. No abnormality was found in the respiratory and circulatory systems. The child was too weak to sit up. A definite wrist drop and a pronounced foot drop with fixed plantar flexion were present on both sides. The ocular fundi were normal. There was no reaction to the von Pirquet test. A blood count made on February 8 revealed that the red blood cells numbered 3,460,000, the white blood cells 5,800, and the stippled cells 107,000 per cubic millimetre; the hæmoglobin value was 45%; basophilic cells were present in large numbers. On February 9 the lead content of the urine was 0·02 milligramme per litre, and on March 20 it was 0·08 milligramme per litre. On February 9 X ray examination revealed that the ribs were of greatly increased opacity; there was evidence of "chalky bones", and bands of increased density were seen at the epiphyseal ends of the diaphyses. The femora were seen to be bottle-shaped at the lower ends for one-third of their length. The changes were most pronounced in the ribs and femora, and the appearances suggested "marble bones".

A further blood count, made on April 8, revealed that the red blood cells numbered 4,040,000 and the white blood cells 10,050 per cubic millimetre; the stippled cells were abundant and the hæmoglobin value was 50%.

The child's two elder brothers and his mother were examined. In the case of the mother, a blood count revealed that the red blood cells numbered 3,760,000 per cubic millimetre, and that no punctate basophilia was present; the hæmoglobin value was 65%.

In the case of the eldest boy, aged twelve years, X ray examination revealed a narrow band of absorption at the ends of both radial diaphyses and to a less degree of both ulnar diaphyses. Slight osteosclerosis of the upper ends of the fibular diaphyses, especially the left, was apparent; there was osteosclerosis of the epiphyses of both tibiæ at the epiphyseal line. The changes suggested lead poisoning. A blood count of the same boy revealed that the red blood cells numbered 4,610,000, the white blood cells 8,500, and the stippled cells 78,800 per cubic millimetre, and that large numbers of basophilic cells were present; the hæmoglobin value was 67%.

In the case of the second boy, aged nine years, X ray examination revealed that the lower ends of the femora and the upper ends of the fibulæ and tibiæ were expanded, suggesting the "clubbing" of "marble bones", and small areas of increased osteosclerosis were seen at the lower ends of the diaphyses of the right radius and ulna; the condition suggested an aberrant case of "marble bones". A blood count revealed that the red blood cells numbered 4,260,000, the white blood cells 10,300, and punctate basophilic cells 33,000 per cubic millimetre; the hæmoglobin value was 59%.

Pericarditis with Purulent Effusion.

DR. LINDSAY DEY showed a boy who had been admitted to hospital on January 22, 1937, with a history of weariness of three weeks' duration. At the time of admission the child was cyanosed and had grunting respiration; the heart was greatly enlarged to the left and right. The heart sounds were faint and the apex beat diffuse. A blood count revealed that the erythrocytes numbered 4,800,000 and leucocytes 27,400 per cubic millimetre. Of the leucocytes, 74% were polymorphonuclear cells, 25% lymphocytes and 1% monocytes. X ray examination revealed that the heart was greatly enlarged, filling most of the chest. Fluid from the pericardium was found to contain Gram-positive cocci in chains and non-hæmolytic streptococci.

On February 4 drainage of the pericardium was carried out. On February 22 X ray examination revealed a large collection of fluid or pus in the left pleural cavity, as well as changes suggestive of bronchopneumonia at the base of the right lung. The heart was partly obscured, but did not appear unduly enlarged. On February 24 straw-coloured fluid was obtained by needling from the left side of the chest. X ray examination on March 22 revealed that the cardiac shadow was slightly larger than normal, but pericardial effusion was not definitely suggested. Irregular dulness at the base of the left lung was observed; this suggested the presence of an incompletely resolved pneumonia in the lower lobe of the left lung, probably accompanied by a small inter-lobar collection of fluid.

Levi-Lorain Type of Adenohypophyseal Dystrophy Treated by Injections of Growth Factor.

DR. LORIMER DODS showed a boy, aged eleven years, suffering from the Levi-Lorain type of adenohypophyseal dystrophy, who had been treated at intervals since the age of six years by injections of adenohypophyseal growth factor. An account of this case was published in THE MEDICAL JOURNAL OF AUSTRALIA in the issue of August 14, 1937.

Congenital Saccular Bronchiectasis.

DR. LORIMER DODS and DR. R. J. TAYLOR showed a girl, aged four years, who had been admitted to hospital on March 22, 1937, suffering from congenital saccular bronchiectasis. She came from a family of eight children, all others of whom were healthy except one, who was subject to fits. Nothing of interest was learned from the child's previous history. The present illness had been of two to three years' duration; the child had had a cough, with copious sputum, troublesome chiefly in the morning and at night, and she had been losing weight.

X ray examination revealed a mottled, cystic, spongy appearance of the whole of the lower half of the right lung; similar changes were observed on the left side to a much smaller degree. A diagnosis of advanced bronchiectasis, probably accompanying some congenital cystic condition, was made. X ray examination of the fingers and toes revealed no involvement of the phalanges; clubbing of fingers appeared to be confined to the soft tissues. The lining mucosa of both antra, especially the left, appeared somewhat hyperplastic. Pigmented nævi were present in the skin. Numerous polymorphonuclear pus cells and Gram-positive cocci were observed in smears of the sputum; no tubercle bacilli were seen. Streptococci and small numbers of *Micrococcus catarrhalis* were found in cultures from the sputum.

Birth Fracture.

DR. P. L. HIPSLEY showed a female infant, aged fourteen months, who had at birth sustained a fracture of the middle of the shaft of the humerus, with some associated angulation of fragments. Instrumental delivery had been necessary, as the fœtus had presented by the head and the shoulders had been impacted. The limb had been put up in an abduction splint, and X ray examinations had later been made at intervals of several months. The final examination revealed no trace of the fracture; clinically, the result was perfect.

Congenital Stricture of the Rectum.

Dr. Hipsley's next patient was a girl, aged five years, who had had a congenital stricture of the rectum. She had been admitted to hospital on June 6, 1932, at the age of seven months. Since the age of six weeks, the child had had practically no normal bowel action; she had been constipated, this condition being relieved at times by diarrhœa accompanied by abdominal pain. The child had always strained at defæcation, and the stools had been clay-coloured; the condition had been thought to be Hirschsprung's disease accompanied by abdominal distention. It was relieved by bowel wash-outs and the passage of sounds and bougies; the diet was carefully regulated. On November 5, 1935, the stricture was incised with a diathermy knife, and in October, 1936, portion of the sacrum was removed and colostomy was performed.

Hydrencephalocele.

DR. H. G. HUMPHRIES showed a male infant, aged eight days, who had been born with a large hydrencephalocele; delivery had been difficult and forceps had been necessary. At operation, performed on April 16, 1937, the mass was amputated close to the skull; it did not appear to communicate with the intracranial space. Examination of the specimen showed it to be a large cystic tumour, fifteen centimetres long and twelve centimetres broad across its widest part, with a pedicle, four centimetres in diameter, attached to its upper pole. The area around the point of attachment contained islands of hair-bearing skin, which gradually faded into the soft vascular tissue composing the outer wall of the sac. Examination of the cut surface of the pedicle revealed a granular, fatty layer beneath the skin, followed by a layer of connective tissue; beneath this was a narrow layer of muscular tissue, covered on its inner surface by a shiny membrane, which lined the whole inner wall of the sac. At the time of the meeting histological examination was not complete; but Dr. Humphries said that there appeared to be a small amount of cerebellar tissue in the thick area close to the pedicle.

Osteomyelitis of the Femur.

Dr. Humphries also showed a girl, aged two years, who was suffering from osteomyelitis of the left femur. At the time of her admission to hospital the child had suffered from sores on the left forearm and on the right arm for one week. She had become sick four days previously, swelling of the left thigh and fever occurring. At the time of admission the child was very sick; the left thigh was swollen and very tender to the touch from the knee to the hip joint; there was complaint of pain if the left hip joint was moved in any direction. The skin was normal in colour and there were no enlarged lymphatic glands.

At operation, which was performed four hours after the child's admission to hospital, an incision was made down to the anterior surface of the upper end of the left femur; no pus was found under the periosteum. The bone was drilled; no pus was found in the medullary cavity. A swabbing was taken from the medullary cavity and a tube was inserted. The left hip joint was needled, but no pus was found. *Staphylococcus aureus* was obtained in culture from the swabbings. On March 18 an attempt at culture of organisms from the blood was made without success. On March 20 there was a profuse purulent discharge from the tube and the child was placed on a Hamilton's frame. X ray examination made on April 6 revealed involvement of the lower seven-eighths of the shaft of the femur. Immediately above this was a large area of absorption containing multiple small sequestra. The joints were not involved.

Microtia.

DR. RAMSAY BEAVIS showed two patients suffering from microtia. The first of these was a male, aged six months, whose right ear was badly deformed, but whose left ear was more normally shaped; both the external auditory canals were absent. The child was obviously very deaf, but it seemed probable that some slight degree of hearing was present.

The child's family history was interesting. The mother had a congenital deformity of the left ear, with absence of the external auditory canal; she was totally deaf in that ear. She had a branchial fistula in the left side of her neck, and she said that she had been unable to swallow solids until she was seven years of age. Dr. Beavis thought that some congenital narrowing of the œsophagus was probably present also. No other members of the mother's family had such abnormalities.

The first child, a female, had had a similar condition to that of the patient; but both ears had been affected and

the child had been deaf and dumb. The mother said that the ears had been more normal in appearance than those of the patient, but both external auditory canals had been absent. The left tear duct had also been obstructed and infected, and the child had been unable to swallow solid food of any description, so that it seemed likely that some congenital narrowing of the œsophagus had also been present. She had died of malnutrition at the age of four years. The second child, a male, aged four years, and the third child, a female, aged eighteen months, were normal in every way. The patient was the fourth child.

Dr. Beavis's second patient was an infant, aged four and a half months, who had microtia of the right ear, with absence of the external auditory canal, but whose left ear was normal. The right side of the child's face was much smaller than the left. Nothing of interest was learned from the family history.

Perforation of the Tegmen Tympani.

DR. NORMAN MEACLE showed a boy, aged four years, who was suffering from perforation of the *tegmen tympani*. On April 2, while the child was playing on the floor, his head fell against a buckle, the spike of which entered his ear. Soon afterwards the mother noticed a watery discharge from the ear, and the child appeared to be in pain. Examination revealed a perforation of the right eardrum, with a profuse discharge of clear fluid. No abnormality was detected in the nervous or other systems. On April 5 the discharge from the ear was still profuse and watery, but it was a little stained with blood; on April 10 the discharge was less in quantity, but yellowish in colour; the child's general condition was unchanged. On April 16 the discharge was very much smaller in quantity and obviously purulent; the child's general condition was excellent. Biochemical examination of the discharge made on April 3 revealed that the chlorides present amounted to 775 milligrammes per hundred cubic centimetres of material; there was no reaction to the globulin test. Microscopic examination of the discharge on April 10 revealed a moderate number of polymorphonuclear pus cells, some *Staphylococci aurei* and a Gram-positive bacillus, which was later found to be a diphtheroid giving no reaction to the fermentation test for Klebs-Löffler bacillus. Dr. Meacle said that the prognosis was guarded on account of the possibility of intracerebral complications.

Xeroderma Pigmentosum.

DR. G. NORRIE showed a female patient, aged twelve years, who was suffering from *xeroderma pigmentosum*. The mother had first noticed, when the child was about one year old, that she was very susceptible to the sunlight and freckled readily. The freckles did not disappear, but became more numerous and noticeable as time went on. The face, neck and arms were particularly affected, the legs slightly; that is, the parts of the body exposed to sunlight were affected. Later, thickened, raised patches appeared and became more numerous. The patient was otherwise healthy; she had a younger brother who was not affected.

The child had first been seen in the out-patient department of the hospital some two years previously. Her face, neck and arms were covered with keratotic patches. Patches of pigmentation, telangiectases, and small atrophic areas of the skin were seen. The bases of some of the keratotic areas were thickened and a cutaneous horn was present on the cheek. A basal-celled epithelioma with ulceration and crusting was observed on the forehead and a growth on the conjunctiva of the left eye.

Dr. Norrie said that treatment had consisted largely in an effort to protect the child from the sunlight as far as possible. She wore a large hat with a veil, long-sleeved frocks, gloves and stockings. Treatment with radium had been very effective, some thirty lesions having been treated successfully. The growth on the conjunctiva had been removed surgically. The child was reporting regularly for treatment, and it was hoped in this way to keep the condition in check, but the prognosis was, of course, bad.

(To be continued.)

NOMINATIONS AND ELECTIONS.

THE undermentioned has been elected a member of the Victorian Branch of the British Medical Association:

Wilson, Thomas Edward, M.B., B.S., 1936 (Univ. Melbourne), Royal Melbourne Hospital, Lonsdale Street, Melbourne, C.1.

THE undermentioned have applied for election as members of the Queensland Branch of the British Medical Association:

Aaron, Kurt, L.R.C.P., L.R.C.S., 1937 (Edinburgh), L.R.F.P. and S., 1937 (Glasgow), Brisbane Hospital, Brisbane.

Meyer, Moritz, L.R.C.P., L.R.C.S., 1937 (Edinburgh), L.R.F.P. and S., 1937 (Glasgow), Holyrood Hotel, Gregory Terrace, Brisbane.

Correspondence.

MALARIA AND ITS TREATMENT BY THE GENERAL PRACTITIONER.

SIR: From his letter in the journal of August 28, Dr. Carl Gunther would have us believe that Professor Nocht and his collaborators are a "parcel of fools".

It is regrettable that Dr. Gunther should be assisting in the propaganda for the use of Dutch quinine by the Dutch Bureau.

Yours, etc.,

227, Macquarie Street, Sydney,
August 28, 1937.

A. E. FINCKH.

Proceedings of the Australian Medical Boards.

NEW SOUTH WALES.

THE undermentioned have been registered, pursuant to the provisions of the *Medical Act*, 1912 *and* 1915, of New South Wales, as duly qualified medical practitioners:

Lush, Studley Woollcott, M.B., B.S., 1937 (Univ. Sydney), Lewisham Hospital, Lewisham.

Varvaressos, Demetrios, L.R.C.P., L.R.C.S., 1937 (Edinburgh), L.R.F.P. and S., 1936 (Glasgow), 61, Latimer Road, Bellevue Hill.

QUEENSLAND.

THE undermentioned have been registered, pursuant to the provisions of *The Medical Acts*, 1925 *to* 1935, of Queensland, as duly qualified medical practitioners:

Aaron, Kurt, L.R.C.P., L.R.C.S., 1937 (Edinburgh), L.R.F.P. and S., 1937 (Glasgow), Brisbane.

Meyer, Moritz, L.R.C.P., L.R.C.S., 1937 (Edinburgh), L.R.F.P. and S., 1937 (Glasgow), Brisbane.

TASMANIA.

THE undermentioned have been registered, pursuant to the provisions of the *Medical Act*, 1918, of Tasmania, as duly qualified medical practitioners:

Morgan, John Wyndham, M.B., B.S., 1911 (Univ. Melbourne), Strahan.

O'Toole, Cyril Paul, L.Lm.R.C.P., L.Lm.R.C.S., 1927 (Ireland), Lachlan Park.

Books Received.

ORGANIZATION, STRATEGY AND TACTICS OF THE ARMY MEDICAL SERVICES IN WAR, by T. B. Nicholls, M.B., Ch.B., with a foreword by Lieutenant-General Sir James A. Hartigan, K.C.B., C.M.G., D.S.O., D.Ch., K.H.P.; 1937. London: Baillière, Tindall and Cox. Royal 8vo, pp. 386. Price: 10s. 6d. net.

POCKET MONOGRAPHS ON PRACTICAL MEDICINE. FAILURE OF THE HEART AND CIRCULATION, by T. East, M.A., D.M., F.R.C.P.; 1937. London: John Bale, Sons and Curnow Limited. Foolscap 8vo, pp. 138. Price: 2s. 6d. net.

PHYSICIANS AND MEDICAL CARE, by E. L. Brown; 1937. New York: Russell Sage Foundation. Large crown 8vo, pp. 209. Price: 75 cents net.

LEAGUE OF NATIONS PUBLICATIONS. BULLETIN OF THE HEALTH ORGANIZATION; Volume VI, Number 1. Geneva: Publications Department of the League of Nations; Australia: H. A. Goddard Limited. Royal 8vo, pp. 127.

THE OVA OF ASCARIS MEGALOCEPHALA, by C. E. Allen, L.D.S., D.D.Sc., F.I.C.D.; 1937. Australia: Ramsay Publishing Proprietary Limited. Double crown 8vo, pp. 115, with illustrations. Price: 21s. net.

RESEARCH MONOGRAPHS OF THE AMERICAN ORTHOPSYCHIATRIC ASSOCIATION. No. I: INTRODUCTION TO THE RORSCHACH METHOD. A MANUAL OF PERSONALITY STUDY, by S. J. Beck, Ph.D., with a preface by F. L. Wells, Ph.D.; 1937. Chicago: The American Orthopsychiatric Association. Double crown 8vo, pp. 290.

RESEARCH MONOGRAPHS OF THE AMERICAN ORTHOPSYCHIATRIC ASSOCIATION. No. II: STUDIES IN SIBLING RIVALRY, by D. M. Levy, M.D.; 1937. Chicago: The American Orthopsychiatric Association. Double crown 8vo, pp. 96.

THE AVITAMINOSES: THE CHEMICAL, CLINICAL AND PATHOLOGICAL ASPECTS OF THE VITAMIN DEFICIENCY DISEASES, by W. H. Eddy, Ph.D., and G. Dalldorf, M.D.; 1937. London: Baillière, Tindall and Cox. Medium 6mo, pp. 348, with 29 plates. Price: 20s. net.

MUIR'S BACTERIOLOGICAL ATLAS, enlarged and rewritten by C. E. van Rooyen, M.D.; Second Edition; 1937. Edinburgh: E. and S. Livingstone. Demy 8vo, pp. 106. Price: 15s. net.

PRINCIPLES OF MEDICAL STATISTICS, by A. B. Hill, D.Sc., Ph.D.; 1937. London: The Lancet Limited. Demy 8vo, pp. 179. Price: 6s. net.

Diary for the Month.

SEPT. 7.—New South Wales Branch, B.M.A.: Organization and Science Committee.
SEPT. 10.—Queensland Branch, B.M.A.: Council.
SEPT. 14.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
SEPT. 15.—Western Australian Branch, B.M.A.: Branch.
SEPT. 21.—New South Wales Branch, B.M.A.: Ethics Committee.
SEPT. 22.—Victorian Branch, B.M.A.: Council.
SEPT. 23.—New South Wales Branch, B.M.A.: Clinical Meeting.
SEPT. 24.—Queensland Branch, B.M.A.: Council.
SEPT. 28.—New South Wales Branch, B.M.A.: Medical Politics Committee.
SEPT. 30.—South Australian Branch, B.M.A.: Branch.
SEPT. 30.—New South Wales Branch, B.M.A.: Branch.
OCT. 1.—Queensland Branch, B.M.A.: Branch.
OCT. 5.—New South Wales Branch, B.M.A.: Council (Quarterly).

Medical Appointments Vacant, etc.

For announcements of medical appointments vacant, assistants, *locum tenentes* sought, etc., see "Advertiser," pages xx to xxii.

MACKAY HOSPITALS BOARD, MACKAY, QUEENSLAND: Resident Medical Officer.

SAINT MARGARET'S HOSPITAL FOR WOMEN, SYDNEY, NEW SOUTH WALES: Honorary Officers.

SYDNEY HOSPITAL, SYDNEY, NEW SOUTH WALES: Honorary Officers.

THE UNIVERSITY OF MELBOURNE, VICTORIA: Professor of Anatomy.

THE WOMEN'S HOSPITAL, CROWN STREET, SYDNEY, NEW SOUTH WALES: Honorary Ear, Nose and Throat Surgeon.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment referred to in the following table without having first communicated with the Honorary Secretary of the Branch named in the first column, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

BRANCHES.	APPOINTMENTS.
NEW SOUTH WALES: Honorary Secretary, 135 Macquarie Street, Sydney.	Australian Natives' Association. Ashfield and District United Friendly Societies' Dispensary. Balmain United Friendly Societies' Dispensary. Leichhardt and Petersham United Friendly Societies' Dispensary. Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney. North Sydney Friendly Societies' Dispensary Limited. People's Prudential Assurance Company Limited. Phœnix Mutual Provident Society.
VICTORIAN: Honorary Secretary, Medical Society Hall, East Melbourne.	All Institutes or Medical Dispensaries. Australian Prudential Association, Proprietary, Limited. Mutual National Provident Club. National Provident Association. Hospital or other appointments outside Victoria.
QUEENSLAND: Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17	Brisbane Associate Friendly Societies' Medical Institute. Proserpine District Hospital. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.
SOUTH AUSTRALIAN: Secretary, 178 North Terrace, Adelaide.	All Lodge appointments in South Australia. All contract Practice Appointments in South Australia.
WESTERN AUSTRALIAN: Honorary Secretary, 205, Saint George's Terrace, Perth.	All Contract Practice Appointments in Western Australia.

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